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Contemporary Treatment of Erectile Dysfunction

A Clinical Guide

Humana Press

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Contemporary Treatment of Erectile Dysfunction

A Clinical Guide

Second Edition

Humana Press

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This book is dedicated to our patients, from whom we learn every day, and to our mentors, whom we continually try to emulate. Dr. Köhler would like to thank Dr. Jon Pryor, Dr. Steven K. Wilson, Dr. Robert E. Brannigan, and Dr. Kevin T. McVary. Dr. McVary would like to thank Dr. Chung Lee and Dr. Jack Grayhack, the latter in memoriam.

Foreword

Erectile dysfunction is a common and difficult problem for men, their partners, and families. The field of erectile function study has progressed dramatically in the past two decades. While the progress has been significant, erectile dysfunction was described and treated for centuries with writings about "impotence" and folk remedies for cures described by writers and physicians since the ancient times. There was little progress in the diagnosis and treatment until the second half of the twentieth century. Beginning in the 1940s and 1950s, surgical approaches were developed, but, because of significant morbidity and poor function, were not widely accepted. At the same time, testosterone was developed as a clinical option for men with hypogonadism with only moderate success, as evaluation of the hypogonadal male was lacking. The beginnings of sexual counseling were reported by Kinsey and colleagues in the 1940s and popularized by Masters and Johnson in the 1970s.

The revolution in the study of erectile dysfunction began with a functioning and safe penile implant in 1973 and the introduction of effective medical treatment with the use of intracavernosal injection therapy in 1984. The most significant step forward in treatment and investigation was from the identification of nitric oxide and its vascular smooth muscle effects in the 1980s and subsequently the development and marketing of type 5 phosphodiesterase inhibitors in the late 1990s. The introduction of sildenafil in 1997 and subsequent type 5 phosphodiesterase inhibitors accelerated the basic science and clinical investigation of erectile physiology and treatment of men with significant, bothersome erectile dysfunction.

The second edition of ***Contemporary Treatment of Erectile Dysfunction: A Clinical Guide*** by two excellent contributors to the field of erectile function and dysfunction is a well-organized and complete treatise updating the state of knowledge and future directions in the study and treatment of erectile dysfunction. The editors have organized the most well-known international contributors in each of the areas of male sexual dysfunction. This guide is an excellent resource for clinicians treating men with erectile and other sexual issues and provides the latest, most up-to-date information from authors who are well known in their areas of expertise.

The organization of the guide is logical and provides information on the basic sciences for the student of erectile dysfunction as well as thorough discussions of the evaluation of the man with erectile dysfunction, hypogonadism, Peyronie's disease, priapism, ejaculatory disorders, and psychological effects of male sexual dysfunction. These discussions of evaluation are followed by

psychological, medical, and, finally, surgical treatment options for these patients. The discussion of alternative and complimentary medications is critical for providers who see men for sexual dysfunction, as there is widespread marketing of these products and as there are many patients using these agents.

Contemporary Treatment of Erectile Dysfunction: A Clinical Guide by Drs. Tobias Köhler and Kevin McVary is an essential guide to health care providers treating men whether in a focused men's health practice or as part of a more general medical or urology practice. This latest information about sexual problems in men is well organized, well written, and complete, and this book should be part of the library of all those interested in male sexual dysfunction.

University of North Carolina
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Culley C. Carson III

Preface

Gladly I think of the days
When all my members were limber, all except one.
Those days are certainly gone.
Now all my members are stiff, all except one.

—Goethe

Erectile dysfunction (ED) is highly prevalent and adversely affects the quality of life of both men and women. The pathophysiology of ED remains incompletely understood despite centuries of snake oil cures and current day mass marketing of treatments. This book's second edition builds on its predecessor's state-of-the art description of the evaluation of, pathophysiology of, hormonal evaluation of, oral and local therapies for, psychotherapy for, prosthetics for, and uncertainty in ED. The contributing authors represent some of the world's finest physicians and researchers in their area. Several new chapters are highlighted in this edition, including separate chapters on the profound effects of lifestyle change on sexual function, alternative and internet drugs that affect sexual function, endovascular approaches to ED, penile length considerations, the effect of radiation on erectile function, and optimizing ED research.

Springfield, IL

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Animal Models for the Study of Erectile Function and Dysfunction

1

Carol A. Podlasek

Prostatectomy Models

During prostatectomy surgery to treat prostate cancer, the cavernous nerve (CN), which is a peripheral nerve that innervates the penis, becomes injured due to physical proximity to the prostate gland being removed. In commonly used animal models, the pelvic plexus including the pelvic ganglia, cavernous nerve, hypogastric and pelvic nerve lie directly on top of the prostate capsule of the ventral lobe of the prostate. While removing the prostate, the cavernous nerve can undergo crush or resection injury and there is the additional potential for tension injury to the pelvic ganglion. Animal models attempt to mimic the human condition by crushing, resecting, cauterizing, or freezing the CN.

The Sprague Dawley rat and C57BL/6J mice are frequently used animal models in which to induce cavernous nerve injury (Table 1.1). It is proposed that crushing of the CN more closely parallels prostatectomy-induced ED than resection, since only ~10 % of prostatectomy surgeries performed in the USA are not nerve sparing. There are several ways in which the CN can be crushed that have been reported in the literature. The most common are by closing forceps around the CN for 30 s [1], repeated 15 s crushes [2], or a 2 min crush using a hemostat [3]. Bilateral crushing of the CN should be performed greater than 5 mm from the pelvic ganglia since postganglionic neurons can be found a substantial distance from the ganglia. This is an error in the model that can be observed in the literature when crush injury is performed too close to the ganglia to impact all fibers. Some level of CN regeneration occurs within 10 weeks after injury [4]; however, erectile function does not fully recover due to downstream morphological changes in the penis induced by denervation [4].

The resection animal model (Table 1.1) was more commonly used prior to the introduction of nerve sparing techniques. In this bilateral model a small (3–5 mm) section of the CN is removed greater than 5 mm from the pelvic ganglia, in either the rat or the mouse. This is a severe form of nerve injury in which the CN is unlikely to regenerate without intervention. It is unclear from the literature whether crushing and cutting the CN engender the same response in the CN and penis tissues.

Less frequently applied models are electrocautery and freezing models (Table 1.1). It has been shown in clinical studies that cautery use when controlling the vascular pedicle and dissecting the neurovascular bundle during robotic laparoscopic radical prostatectomy [5] can cause CN damage. For the cautery animal model, monopolar electrocautery is performed for 1 s at 350 kHz and 15 W

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Table 1.1 Summary of ED models

Condition	Model	Characteristics, advantages, disadvantages
Prostatectomy	Sprague-Dawley and C57BL/6 J CN crush	CN crush reflects a majority of the injury that occurs with prostatectomy **CN crush performed too close to PG for complete denervation**
	Resection	
	Cauterizing	
	Freezing	
Diabetic	Streptozotocin	Non-insulin dependent Vascular disease and neuropathy
	BB/WOR	Insulin dependent Central and peripheral neuropathy No vasculopathy **Can isolate neuronal changes**
	Db/db	Type 2 Hyperglycemia and elevated insulin Cardiovascular disease and neuropathy
	Zucker	Type 2 Obesity, hyperglycemia, hyperinsulinemia, hyperlipidemia, moderate hypertension Vascular and neural complications **Applicability to human diabetes is a concern because patients do not generally show leptin receptor deficit**
	Alloxan	Permanent glycosuria Neuropathy and cardiovascular complications **High doses required which can damage other organs than the pancreas**
	Long-Evans Tokushima Otsuka (OLETF)	Non-insulin-dependent type 2 Insulin resistance precedes impaired pancreas function Late onset hyperglycemia and mild obesity Neuropathy and cardiomyopathy
Aging	Sprague Dawley	Spontaneously neuropathy and cardiomyopathy (23 %)
	Fischer 344	Spontaneous cardiomyopathy **May not well reflect human condition because of suppressed gonadotropin secretion and Leydig tumors**
	Wistar	Spontaneous cardiomyopathy and suggested neuropathy
	Brown-Norway	Decreased smooth muscle/collagen
Metabolic syndrome	New Zealand white rabbits fed high fat diet	Cholesterol, triglycerides, blood glucose, mean arterial pressure, and visceral fat increase
	Obese-diabetic Zucker	30 % decrease in ICP, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia
	High fat diet fed C57BL/6	60 % calories from fat for 8 weeks ATP synthase alterations contribute to ED
	Phosphoenolpyruvate carboxykinase overexpressing rat	Obesity, hyperinsulinemia, dyslipidemia impaired glucose tolerance associated with peripheral insulin resistance Impaired nitrergic nerve regeneration

(continued)

Table 1.1 (continued)

Condition	Model	Characteristics, advantages, disadvantages
Hypertension	Spontaneously hypertensive (SHR)	Spontaneous hypertension, ED
	Sprague–Dawley Angiotensin II treated	4 weeks of treatment, ED and increased corpora cavernosal contractility, decreased nitrergic relaxation, increased ERK1/2 phosphorylation
	Second hand smoke	8 weeks exposure, hypertension, reduced NOS activity, and nNOS content
High cholesterol	High fat diet fed rabbits and rats (1–2 % cholesterol)	3–6 months of feeding, ~53 % atherosclerosis induction and ED, ED, decreased nNOS and endothelial cells while smooth muscle increased
	Apolipoprotein-E-knockout	Hypercholesterolemia, atherosclerotic lesions **Forms atherosclerotic lesions similar to patients**
Arteriogenic	Bilateral ligation of the iliac arteries	Reduced erectile function, reduced nNOS staining fibers, intracellular deposition of fat and collagen
Hypoxia	Sprague–Dawley CN crush, resection	**It is not possible to determine the contribution of hypoxia alone in these models**
	High-cholesterol diet fed mice	
Radiation	Radiation treated Sprague–Dawley rat	ED, decreased nNOS and smooth muscle, increased inflammatory markers **Time course of decreased ICP development is much longer than CN crush or resection injury**

[6]. Functional analysis by intracavernosal pressure (ICP) measurement decreases in a similar manner to that observed with the CN crush model. Cryo-ablation of the prostate can cause ED due to injury to the CN. There is moderate interest for the use of cryotechnology for the treatment of localized prostate cancer [7, 8]. Therefore an animal model of freezing injury has been developed [9] whereby finely ground dry ice is applied to the CN twice, in 2-min intervals. Freezing the CN resulted in decreased ICP at 1 month with somewhat recovery by 3 months and altered growth factor signaling in the CN [9, 10]. How well this model parallels morphological changes in the penis observed after crush and resection injury is unclear.

The pelvic ganglia regulate blood flow into the penis and thus regulate tumescence. Nerve impulses travel from the pelvic ganglia to the penis tissue via the CN, which is composed of both sympathetic and parasympathetic nerve fibers [11]. Human and rat anatomy are not identical with regard to the CN, which is a discreet bundle in rodents but more closely resembles a network of fibers in humans. While the anatomy is more diffuse in patients, the same general principles of innervation apply to both the human and rat.

Diabetic Models

ED is common in diabetic patients, which are three times more likely to develop ED than non-diabetic men [12, 13]. Men with diabetes develop ED at an earlier age and the incidence of ED may be as high as 75 % in diabetic patients [14]. Oral therapy with PDE5 inhibitors is effective in only a minority of insulin-dependent diabetic cases [15]. Therefore several animal models of type 1 and 2 diabetes, which display vascular and neuronal changes associated with diabetes, have been developed.

Probably the most commonly used diabetic model is the Streptozotocin-induced rat or mouse (Table 1.1) [16]. This is a non-insulin-dependent model of diabetes that displays both vascular disease and neuropathy. Streptozotocin induces concentration-dependent necrosis of the pancreatic β-cells [16], resulting in a diabetic condition that resembles adult onset diabetes [17]. The β-cells become insensitive to glucose and do not secrete insulin in response to glucose stimulation within the range of 5.5–22 mM [18]. However, stimulation with glyceraldehyde does elicit insulin release, suggesting a block in glucose metabolism in the early steps of glycolysis [18], in

response to Streptozotocin treatment. The lowest effective streptozotocin dose to induce a similar chemical state to diabetes in patients is 25 mg/kg [19]. However, concentrations as high as 100 mg/kg have been reported [19], as well as multiple Streptozotocin injections. Axonal dwindling, decreased fiber size, and ultrastructural lesions in Schwann cells have been demonstrated in this model, indicating neuropathy [20–22]. Long-term (6–12 months) exposure results in neurons of a smaller caliber being preferentially affected; neurons of this size are representative of sensory and autonomic innervation [17]. Vascular disease is also present in this model as shown by induction of cardiomyopathy including reduced aortic output, ventricular pressure, and cardiac work [23]. Early studies by Sachs et al. [24] suggested that measures of sexual motivation, and performance, remained unchanged in this model, and therefore it may not be the best model of diabetic ED. However, deceased ICP was later well documented [25] along with decreased smooth muscle and endothelium [26], indicating ED.

The BB/WOR rat model is a naturally occurring rat model of type 1 diabetes that closely mimics the characteristics of human diabetes (Table 1.1). The BB/WOR rat demonstrates both central and peripheral neuropathy, with severe impairment of spinal sexual reflexes and peripheral neuropathic changes in hypogastric and motor pudendal nerve fibers [27]. Approximately 50 % of BB/WOR diabetic rats have profoundly decreased erectile function [27, 28] and abundant remodeling of the corpora cavernosa including a ~12-fold increase in apoptosis [28]. The onset of diabetes occurs between 60 and 120 days [28]. The advantage of this model is that it is characterized by neuropathy without the vasculopathy present in other diabetic models. This allows for the study of changes that occur due to neuropathy alone. Atherosclerosis and microangiopathy, key features of vasculopathy, are absent in the BB/WOR rat [29]. The high cost of this animal model prohibits study and leads to underutilization of this model.

The C57BL/KsJ-db/db (db/db) strain is a genetically diabetic mouse strain that exhibits hyperglycemia and elevated insulin abundance (Table 1.1) [30]. This is a mouse model of type 2 diabetes in which the proportion of beta cells is decreased, with irregular islet architecture and degenerative and hypertrophic changes apparent in individual beta cells [30]. Cardiovascular disease is apparent in this model including progressive damage to the ventricular myocytes and intramural small arteries [31]. Neuropathy was also identified, including degenerative changes in perivascular nerve endings [31], severely decreased motor nerve conduction velocity (early phase of diabetes), and absence of large, myelinated fibers with morphological features indicative of axonal atrophy [32, 33]. Morphometric changes occurred after 20 weeks of diabetes in myelinated and unmyelinated fibers [33]. Axonal degeneration, disruption of myelin, accumulation of electro-dense material in axons, satellite cells and Schwann cells, increased frequency of pi granules of Reich in Schwann cells, enlarged mitochondria, and proliferated and thickened Schwann cell basal laminae were observed [34]. Morphological indications of Schwann cell hyperplasia, hypertrophy, and axonal sprouting support the idea of a continuous cycle of axonal degeneration and regeneration [34] in this diabetic model. These neuropathic changes can be prevented by diet restriction preventing obesity in the db/db mouse [35]. The db model has been introduced to several different mouse strains and in combination with other mutations such as endothelial nitric oxide synthase, and obese spontaneous mutation, resulting in varying degrees of diabetes severity and obesity (Jackson Laboratories). This model has been used infrequently to study contractility, Rho/ROCK signaling, and neuropathy in erectile function [36–39].

The Zucker rat model (ZDF) is a spontaneously occurring rat model of type 2 diabetes (Table 1.1). This model is also characterized by obesity, hyperglycemia, hyperinsulinemia, hyperlipidemia, and moderate hypertension [40] and is commonly used to study obesity and metabolic syndrome. Diabetes in this strain initially appears with modest hyperglycemia and profound hyperinsulinemia, representing a state of considerable insulin resistance. Over time the pancreas becomes exhausted, with decreased

insulin secretion and increased plasma glucose. This model displays both vascular and neural complications. Cardiomyopathy presents as defects in both diastolic and systolic function [41]. Neuropathy accompanies hyperglycemia development [42]. Motor nerve conduction velocity is reduced, preceding impaired vascular relaxation of epineurial arterioles of the sciatic nerve [43, 44]. The applicability of this model to human diabetes is a concern because of the recessive homozygous mutation in the leptin receptor that results in loss of function and severe hyperphagia [45, 46]. Leptin is believed to play a role in metabolic syndrome development [47–51]; however, since type 2 diabetic patients generally do not show a leptin receptor deficit, this model does not well parallel the human condition [42]. This led to the development of the Zucker diabetic Sprague–Dawley rat (ZDSD) [45, 46], which has a predisposition for obesity and develops diabetes between 15 and 21 weeks of age. The ZDSD rat has an intact leptin signaling system [45] so is more comparable to diabetic patients. The ZDSD rat model is characterized by reduced conduction velocity in comparison to Sprague–Dawley rats in both motor and sensory fibers at 34 weeks of age [42].

Another chemical model of diabetes less commonly utilized in ED studies is the alloxan-injected rat or rabbit (Table 1.1). Alloxan is closely related to purines chemically and it is found in the body during normal metabolism [52]. Permanent glycosuria can be induced in rats by injection of alloxan, caused by necrosis of the pancreatic islet cells [52]. This model may be less frequently utilized because higher doses of alloxan are required in rabbits (100 mg/kg) and rats (140 mg/kg) [53] in order to induce diabetes, and at higher doses alloxan can damage other organs than the pancreas (such as the kidney) and can result in death within a few hours due to effects on circulation [52]. This model displays neuropathy as shown by a reduction of conduction velocity speed in the fastest fibers, chronic focal Schwann cell damage with regeneration [54], and reduced axonal flow [55]. Cardiovascular complications were also identified including morphological changes in the aorta [56], a decrease in cardiac performance 42 days after alloxan treatment [57], and structural manifestations of cardiomyopathy [58]. This model has been shown to display increased contractility of corpora cavernosal smooth muscle [59], decreased endothelial nitric oxide synthase (eNOS) [60], and eNOS inactivation by a glycosylation mechanism at Ser-1177, which renders the enzyme unresponsive to fluid sheer stress [53].

Long-Evans Tokushima Otsuka rats (OLETF) are a model of spontaneous non-insulin-dependent type 2 diabetes, in which insulin resistance precedes impaired pancreas function (Table 1.1) [61]. This model expresses late onset hyperglycemia (after 18 weeks), mild obesity, and diabetes which can be divided into three stages of pancreas dysfunction, an early stage (less than 9 weeks) which shows mild lymphocyte infiltration, a hyperplastic stage (10–40 weeks) which shows hyperplastic change and fibrosis in and around islets, and a final stage (more than 40 weeks) which shows atrophy of islets [62]. OLETF rats exhibit reduced motor nerve conduction velocity (tenth month), reduced sciatic nerve blood flow [63, 64], and decreased myelinated fiber size [65]. This model also displays cardiomyopathy as shown by diastolic dysfunction developing after 17 weeks [66]. This model has been used infrequently to study testosterone replacement [67] and angiogenesis [68] effects on ED.

Aging Models

Aging is a significant risk factor for developing ED. The combined prevalence of minimal, moderate, and complete ED is 52 % in men aged 40–70 years [69]. The proportion of sexually active males decreases from 83.7 % (57–64) to 38.5 % (75–85) as men age [70] and in the European Male Aging Study (EMAS), the prevalence of ED increased with age, peaking at 70 [71]. In the Massachusetts Male Aging Study, subject age was the variable most strongly associated with ED [69]. Since ED has a high impact on men's health, animal models are needed to

improve our understanding of how ED develops with age. Unfortunately, there appears to be no one particular model of aging-related ED that stands out as "the" model of choice. With each strain noted below, reduced ICP was noted, indicating reduced erectile function.

Sprague–Dawley rats are commonly used as an aging model to study ED (Table 1.1). This model displays spontaneous neuropathy that is age related in 23 % of male rats [72] and age-related spontaneous cardiomyopathy including myocardial degeneration and fibrosis [73]. In aging Sprague–Dawley rats (18 months) compared to young (10 week) rats, an early study by Burchardt et al. [26] indicated that there was no difference in smooth muscle or endothelial content in young versus old rats. However, when three groups of aging Sprague–Dawley rats (9, 14, and 62 weeks) were compared, it was found that the tunica albuginea became thinner with reduced elastic fibers, the collagen fibers increased while smooth muscle and elastic fibers were decreased [74]. Sprague–Dawley rats aged 6, 12, 18, 24, and 28 months showed progressively decreasing ICP with age [75], unchanging Bak and Bax (pro-apoptotic), and decreasing Bcl-2 and Bcl-x (anti-apoptotic) indicating apoptosis [75]. NOS-I expression and activity were also reduced with age [76], suggesting potential for ED development.

Fischer 344 rats have also been utilized in several ED studies (Table 1.1). However, early work by Gurenewald indicates that this model may not well reflect the human condition of reproductive aging because Fischer 344 rats secrete excessive progesterone and estradiol which suppress gonadotropin secretion [77]. This model also develops Leydig cell hyperplasia or tumors in 100 % of aged rats [77, 78]. Spontaneous cardiomyopathy has been observed in aging Fischer rats [73] as well as corporal veno-occlusive dysfunction at 24 months in comparison to 5 months [79]. Erectile function is reduced by ~30 % with aging, as demonstrated by reduced ICP [79]. Fischer 344 young (5 month) versus aged (20 month) rats have been used to study the effects of L-arginine [80] and testosterone [81] on erectile function. Endothelial NOS phosphorylation was studied in Fischer 344 young (4 month) versus aged (19 month) rats. It was found that aging caused a decrease in phosphorylation of eNOS positive regulatory site (Ser-1177) and an increase in phosphorylation of its negative regulatory site (Thr-495) in the penis [53]. Fischer 344 rats (20 months) were also treated with sildenafil in the drinking water for 45 days, showing decreased fibrosis [82]. It is unclear if the compounding factor of gonadal axis disruption had any significant physiological impact on these studies.

Wistar rats develop spontaneous aging-related cardiomyopathy as in the case with Sprague–Dawley and Fischer 344 rat models (Table 1.1) [73]. This model also develops ultrastructural changes in the plantar and tibial nerves characteristic of demyelination and remyelination [83], suggesting neuropathy. Regeneration after sciatic nerve injury is also delayed in aging Wistar rats, supporting the idea of neuropathy development [84]. Wistar rats (20, 40, and 80 weeks) show increased collagen 3 and 4 that is moderately associated with age [85] and decreased smooth muscle (2, 6, 12, 18, and 24 months) [86], which are characteristic morphological changes associated with ED development in prostatectomy and diabetic animal models.

Another rat model that has been used to study ED is the Brown-Norway rat (Table 1.1). This model does not display the androgen fluctuations that are present in Fischer 344 rats. This model exhibits decreased smooth muscle/collagen ratio, increased ROS and iNOS, and increased smooth muscle apoptosis in the resistance arteries (abdominal aorta, femoral and brachial arteries) and in the penis [87] in old (23–28 months) versus young (6 months) rats.

Metabolic Syndrome Model

Metabolic syndrome comprises a combination of risk factors that contribute to cardiovascular disease and to ED, including obesity, hypertension, and diabetes. The mechanism of how these factors combine to contribute to ED development remains unclear. Therefore animal models are

needed for molecular, physiological, and histological studies. Most of the studies that have been performed in animal models focus on high fat diet treatment of rabbits or the Zucker obese and/or diabetic rat. Mouse models and genetic manipulation have rarely been incorporated into study of metabolic syndrome related ED. A few examples where these models were applied and their effect on ED are mentioned.

Male New Zealand white rabbits were fed a high fat diet consisting of 0.5 % cholesterol and 4 % peanut oil for 12 weeks (Table 1.1). Cholesterol, triglycerides, blood glucose, mean arterial pressure, and visceral fat levels increased [88]. Serum testosterone decreased; however, there were no changes observed in testicular or epididymal histology [88]. Rabbits were fed the same diet, with or without testosterone supplement. High fat diet-induced penile alterations including acetylcholine and electrical field stimulation induced CC relaxation, hyper-responsiveness to the NO donor, SNP, and unresponsiveness to PDE5 inhibitors. Testosterone administration prevented almost all of the penile alterations observed in high fed diet rabbits.

A second animal model used to study metabolic syndrome is the obese-diabetic Zucker rat (Table 1.1). This animal model shows a ~30 % decrease in the erectile response [89]. Sixteen to 20-week-old rats showed that protein kinase C and Rho-kinase contribute to enhanced vasoconstriction of penile smooth muscle identified in this model [90]. Short-term statin therapy may lower RhoA/Rho-kinase expression levels and improve the cavernosal blood pressure response to Rho-kinase inhibition and voltage stimulation, reversing augmented vasoconstriction associated with diabetes and/or hypertension in metabolic syndrome [89].

The obese Zucker rat (nondiabetic) has also been used to study ED development in 17- to 18-week-old rats. This model is characterized by hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and hyperinsulinemia. It was found that insulin-induced relaxation was impaired in penile arteries of this model due to altered NO release through the PI3K pathway and unmasking of a MAPK-mediated vasoconstriction, which contributes to the endothelial dysfunction [91].

The C57BL/6 mice fed a high fat diet have also been used as a model of metabolic syndrome (Table 1.1). In this model, mice are fed a diet with 60 % of the calories derived from fat, for 8 weeks. ATP synthase and p-Akt signaling were studied in this model and it was found that ATP synthase may be a target of lipotoxicity in corpora cavernosal smooth muscle, thus contributing to ED development [92].

The phosphoenolpyruvate carboxykinase overexpressing rat has also been proposed as a model of metabolic syndrome (Table 1.1). This model is characterized by obesity, hyperinsulinemia, dyslipidemia and has impaired glucose tolerance with associated peripheral insulin resistance. Therefore this model displays many of the features that are characteristic of the metabolic syndrome. Impaired regeneration of nitrergic nerves after crush injury was identified in this model despite the lack in reduction of the maximal response to NO donor sodium nitroprusside that was displayed in control rats [93].

Hypertension Model

Hypertension is a risk factor for ED and cardiovascular disease that has been studied as part of the metabolic syndrome and independently to determine contribution to ED development. Men with hypertension have a higher prevalence of ED [69, 94] and the incidence of ED is associated with duration and severity of hypertension [69]. Eight to 10 % of untreated hypertensive patients have ED at the time of hypertension diagnosis [95].

There are several rat models that have been used to study hypertension. Probably the most commonly used model is the spontaneously hypertensive rat (SHR) and normotensive Wistar-Kyoto (WKY) control rats (Table 1.1). The model was developed at the Okamoto, Kyoto School of Medicine in 1963 from outbred Wistar-Kyoto rats with selection for spontaneous hypertension. Erectile function is significantly

lower in this model as measured by ICP in SHR rats versus controls [96, 97]. mRNA expression levels of nNOS and eNOS in the penis are decreased in SHR rats [98]. Major modifications in the distribution of collagen I, III, and V occur in corpora cavernosa and aorta of SHR rats; however, the modifications are detectable sooner in erectile tissue compared with aorta [96]. There are conflicting reports of increased proliferation in the corpora cavernosa and vascular smooth muscle, and of fibrosis [99] and with decreased smooth muscle and increased collagen [100]. Most of the studies reported in the literature have used this model to test various hypertensive drugs [101, 102].

Two less commonly used hypertension models are the Sprague–Dawley rat treated with Angiotensin II by mini-pump for 4 weeks and a second hand smoke model (Table 1.1). Angiotensin II treated rats display ED accompanied by increased corpora cavernosal contractility, decreased nitrergic relaxation, and increased ERK1/2 phosphorylation [103]. In the second hand smoke model, adult (5 month) and old (20 month) Fischer 344 rats were exposed to second hand smoke daily for 8 weeks. This led to induction of a moderate hypertension, reduced NOS activity, and nNOS content. However, erectile function was not affected and neither was eNOS [104].

High Cholesterol Model

Hyperlipidemia is common in ED patients. The prevalence of hypercholesterolemia is 70.6 % in ED versus 52 % in non-ED patients [105]. For every mmol/l increase in total cholesterol there is associated a 1.32 times greater risk of developing ED [106]. The most commonly used animal models to study the effects of high cholesterol on erectile function are high fat diet fed rabbits and rats (Table 1.1). Typically 1–2 % cholesterol is added to standard animal chow and the animals are fed the modified diet for 3–6 months, which results in raised cholesterol levels, lower HDL, and decreased ICP/BP, indicating ED. The rabbit model fed a 1.5 % cholesterol diet for 12 weeks showed a 52.9 % rate of atherosclerosis induction and ED [107]. New Zealand rabbits fed 1 % cholesterol diet were used to study signaling changes in the corpora cavernosa, which showed decreased p-Akt/Akt, VEGF, eNOS, and nNOS [108]. For the rat model, Sprague–Dawley rats were fed a high fat diet for 6 months. This resulted in prostatic enlargement, bladder overactivity, and ED [109]. Rats fed a high fat diet for 5 months resulted in lower ICP/BP, nNOS, and endothelial cells while smooth muscle increased [110].

The Apolipoprotein-E-knockout ($Ap2^{-/-}$) mouse is another model of hypercholesterolemia and atherosclerotic lesions throughout the arterial tree (Table 1.1) [111]. This model has more pronounced hypercholesterolemia with high fat diet feeding [112–116]. The characteristics of ApoE knockout mice are similar to those observed in humans [112, 117]. Thirty- to 35-week-old ApoE mice also display endothelial dysfunction [118, 119]. The advantage of this model is that it forms atherosclerotic lesions similar to those of patients, whereas high fat diet fed rats do not typically develop atherosclerotic plaques [120]. While the high fat diet fed rabbit does develop atherosclerotic lesions, the cost of daily maintenance is prohibitive. The ApoE knockout mouse displays reduced erectile responses at 26 weeks and beyond [121]. When the ApoE knockout mice are fed a 1.25 % cholesterol diet for 2–12 weeks, they showed abnormalities in endothelium-dependent and endothelium-independent vasoreactivity, endothelial content, smooth muscle/collagen ratio, p-eNOS phosphorylation at Ser 1177, nNOS, and cGMP that are duration of diet dependent [122].

Arteriogenic ED Model

Penile arterial insufficiency is commonly associated with hypertension, dyslipidemia, diabetes, pelvic irradiation smoking, and ED [123]. It has been proposed that a progressive, mild intracorporal fibrosis, which also affects the media of the penile arteries, may contribute to vasculogenic ED [124]. An arteriogenic model used to study ED is a surgical model in which bilateral ligation of the iliac arteries is performed in the rat

(Table 1.1). This leads to reduced erectile function [125, 126] and reduced nNOS staining fibers in the dorsal and intracavernosal nerves [126]. Little change in smooth muscle was observed, as well as fibroblast and myofibroblast loss, intracellular deposition of fat and collagen, and fatty degeneration [126]. This model was used to show that Vardenafil treatment can improve the ED found in the ligation group, and can improve the smooth muscle/collagen ratio [127].

Hypoxia Model

It has been suggested that hypoxic conditions may contribute to the development of ED [128–132]. The animal models that have been explored for study of hypoxia are the CN crush [131] or resection [128] rat models and the high-cholesterol diet-induced mouse model (Table 1.1) [133]. While hypoxia is present in all three of these models, it is not possible to determine the contribution from hypoxia alone on erectile function and penile morphology since there is the confounding factor of injury to the CN, which has been shown to cause the morphological changes identified in these models. Whether hypoxia contributes to these processes can only be determined under conditions where hypoxia is present without other risk factors for ED. Perhaps an ischemic model would be better suited to determine contribution from hypoxia on erectile function and physiology.

Drug Induced

So far only one model of drug-induced ED has been probed in an animal model. That is the methamphetamine fed Sprague–Dawley rat in which acute administration of methamphetamine causes decreased ICP/BP, indicating ED development (Table 1.1) [134]. Chronic administration results in 50 % reduction in ICP/BP [134]. The observed ED can be reversed with tadalafil treatment [134], suggesting that methamphetamine or amphetamine associated ED in patients may benefit from PDE5i treatment.

Radiation-Induced ED

Radiation is commonly used as a treatment for prostate cancer, and this results in ED that develops progressively in 50 % of men 3–5 years after external beam radiotherapy [135, 136]. Clinical studies indicate reduced penile blood flow, suggesting vascular injury as an underlying feature of ED development in patients [137–139].

Efforts in the last few years have focused on developing a radiation induced ED animal model that reflects the type of focused radiation treatment that is utilized in patients [140]. The most recent model utilizes irradiated Sprague–Dawley rats that receive prostate-confined radiation in a single 20 Gy fraction (Table 1.1) [141]. In this model, radiation induced ED decreases nNOS in the penis and pelvic ganglia, decreases smooth muscle, and increases inflammatory markers [141–143]. The time course of decreased ICP/BP development is much longer than that observed after CN crush or resection injury in which ED is observed within the first 1–2 days after injury, in comparison to 4 weeks for the radiated model. A longer time line of decreased nNOS was also observed with radiation treatment [144] at 4 weeks and beyond. Smooth muscle did not decrease until 9 weeks [144]. Since the time course of neuronal injury and penile morphology changes is significantly longer than that observed in CN crush and resection models, it is unclear if the mechanism of injury is similar in these models.

Conclusion

There are a plethora of animal models that have been used to study the development of ED, with variable success and similarity to the human condition. Careful selection of an appropriate model for study, keeping in mind potential neuropathic and vascular changes and gonadal dysfunction that may develop with age in a percentage of animals of each model type, is critical. It is also essential when selecting an appropriate model to study animals that are adult, and no longer undergoing developmental changes or growth that can

confound findings. What is considered "adult" in rats is commonly misconstrued since penile weight is still increasing from 12 to 16 weeks (84–112 days) in the rat, androgen receptor has not reached its final minimal level until between 12 and 16 weeks (112 days), and genes important for penile development are still changing at 90 days after birth and do not reach their adult levels until postnatal day 120 in Sprague–Dawley rats [145, 146]. This is disconcerting given the observation that many investigators utilize rats under 100 days old for their studies, without consideration of how developmental factors will impact their findings. Further studies are needed to understand the contribution of specific risk factors to the pathogenesis and physiological alterations that contribute to ED development.

References

1. Angeloni NL, Bond CW, Tang Y, Harrington DA, Zhang S, Stupp SI, McKenna KE, Podlasek CA. Regeneration of the cavernous nerve by sonic hedgehog using aligned peptide amphiphile nanofibers. Biomaterials. 2011;32:1091–101.
2. Weyne E, Albersen M, Hannan JL, Castiglione F, Hedlund P, Verbist G, De Ridder D, Bivalacqua TJ, Van der Aa F. Increased expression of the neuroregenerative peptide galanin in the major pelvic ganglion following cavernous nerve injury. J Sex Med. 2014;11:1685–93.
3. Burnett AL, Sezen SF, Hoke A, Caggiano AO, Iaci J, Lagoda G, Musicki B, Bella AJ. GGF2 is neuroprotective in a rat model of cavernous nerve injury-induced erectile dysfunction. J Sex Med. 2015;12(4):897–905.
4. Nangle MR, Keast JR. Reduced efficacy of nitrergic neurotransmission exacerbates erectile dysfunction after penile nerve injury despite axonal regeneration. Exp Neurol. 2007;207:30–41.
5. Ahlering TE, Skarecky D, Borin J. Impact of cautery versus cautery-free preservation of neurovascular bundles on early return of potency. J Endourol. 2006;20:586–9.
6. Song LJ, Zhu J-Q, Xie M-K, Wang Y-C, Li H-B, Cui Z-Q, Lu H-K, Xu Y-M. Electrocautery-induced cavernous nerve injury in rats that mimics radical prostatectomy in humans. BJU Int. 2014;114:133–9.
7. Hale Z, Miyake M, Palacios DA, Rosser CJ. Focal cryosurgical ablation of the prostate: a single institute's perspective. BMC Urol. 2013;13:2.
8. Kim FJ, Cerqueira MA, Almeida JC, Pompeo A, Sehrt D, Calheiros JM, Martins FA, Molina WR. Initial Brazilian experience in the treatment of localized prostate cancer using a new generation cryotechnology: feasibility study. Int Braz J Urol. 2012;38:620–6.
9. El-Sakka AI, Hassan MU, Bakircioglu ME, Pillarisetty RJ, Dahiya R, Lue TF. Possible molecular mechanisms of cryoablation-induced impotence in a rat model. Urology. 1998;52:1144–50.
10. Bakircioglu ME, Lin CS, Fan P, Sievert KD, Kan YW, Lue TF. The effect of adeno-associated virus mediated brain derived neurotrophic factor in an animal model of neurogenic impotence. J Urol. 2001;165:2103–9.
11. Modder J, Podlasek CA, McVary KT. Pathophysiology of erectile dysfunction following radical prostatectomy. In: Mulhall J, editor. Sexual function in the prostate cancer patient, Humana, vol. 268. NJ: Totowa; 2009. p. 34–47.
12. McCulloch DK, Campbell IW, Wu FC, Clarke B, Prescott RJ. Impotence in diabetic and non-diabetic hospital outpatients. Br Med J. 1980;281:1216.
13. Eardley I, Fisher W, Rosen RC, Niederberger C, Nadel A, Sand M. The multinational men's attitudes to life events and sexuality study: the influence of diabetes on self-reported erectile function, attitudes and treatment-seeking patterns in men with erectile dysfunction. Int J Clin Pract. 2007;61:1446–53.
14. Hakim LS, Goldstein I. Diabetic sexual dysfunction. Endocrinol Metab Clin North Am. 1996;25:379–400.
15. Perimenis P, Markou S, Gyftopoulos K, Athanasopoulos A, Giannitsas K, Barbalias G. Switching from long-term treatment with self-injections to oral sildenafil in diabetic patients with severe erectile dysfunction. Eur Urol. 2002;41:387–91.
16. Junod A, Lambert AE, Orci L, Pictet R, Gonet AE, Renold AE. Studies of the diabetogenic action of streptozotocin. Proc Soc Exp Biol Med. 1967;126:201.
17. Mattingly GE, Fischer VW. Peripheral neuropathy following prolonged exposure to streptozotocin-induced diabetes in rats: a teased nerve fiber study. Acta Neuropathol. 1983;59:133–8.
18. Giroix MH, Portha B, Kergoat M, Bailbe D, Picon L. Glucose insensitivity and amino-acid hypersensitivity of insulin release in rats with non-insulin-dependent diabetes. A study with the perfused pancreas. Diabetes. 1983;32:445–51.
19. Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin: relationship of dose to metabolic response. J Clin Invest. 1969;48:2129–39.
20. Jakobsen J. Axonal dwindling in early experimental diabetes. II. A study of isolated nerve fibres. Diabetologia. 1976;12:547–53.
21. Jakobsen J, Lundbaek K. Neuropathy in experimental diabetes: an animal model. Br Med J. 1976;2:278–9.

22. Bestetti G, Rossi GL, Zemp C. Changes in peripheral nerves of rats four months after induction of streptozotocin diabetes. A qualitative and quantitative study. Acta Neuropathol. 1981;54:129–34.
23. Schaffer SW, Tan BH, Wilson GL. Development of a cardiomyopathy in a model of noninsulin-dependent diabetes. Am J Physiol. 1985;248:H179–85.
24. Sachs BD, Baum MJ, Melman A. Normal sexual behavior and penile reflexes in long-term diabetic male rats. Arch Androl. 1982;9:351–3.
25. El-Sakka AI, Lin CS, Chui RM, Dahiya R, Lue TF. Effects of diabetes on nitric oxide synthase and growth factor genes and protein expression in an animal model. Int J Impot Res. 1999;11:123–32.
26. Burchardt T, Burchardt M, Karden J, Buttyan R, Shabsign A, de la Taille A, Ng PY, Anastasiadis AG, Shabsigh R. Reduction of endothelial and smooth muscle density in the corpora cavernosa of the streptozotocin induced diabetic rat. J Urol. 2000; 164:1807–11.
27. McVary KT, Rathnau CH, McKenna KE. Sexual dysfunction in the diabetic BB/WOR rat: a role of central neuropathy. Am J Physiol. 1997;272: R259–67.
28. Podlasek CA, Zelner DJ, Harris JD, Meroz CL, Tang Y, McKenna KE, McVary KT. Altered sonic hedgehog signaling is associated with morphological abnormalities in the penis of the BB/WOR diabetic rat. Biol Reprod. 2003;69:816–27.
29. Wright Jr JR, Yates AJ, Sharma HM, Thibert P. Pathological lesions in the spontaneously diabetic BB Wistar rat: a comprehensive autopsy study. Metabolism. 1983;32:101–5.
30. Boquist L, Hellman B, Lemmark A, Taljedal IB. Influence of the mutation "diabetes" on insulin release and islet morphology in mice of different genetic backgrounds. J Cell Biol. 1974;62:77–89.
31. Giacomelli F, Wiener J. Primary myocardial disease in the diabetic mouse. An ultrastructural study. Lab Invest. 1979;40:460–73.
32. Sima AA, Robertson DM. Peripheral neuropathy in mutant diabetic mouse [c57BL/Ks (db/db)]. Acta Neuropathol. 1978;41:85–9.
33. Robertson DM, Sima AA. Diabetic neuropathy in the mutant mouse [c57BL/ks(db/db)]: a morphometric study. Diabetes. 1980;29:60–7.
34. Carson KA, Bossen EH, Hanker JS. Peripheral neuropathy in mouse hereditary diabetes mellitus. II. Ultrastructural correlates of degenerative and regenerative changes. Neuropathol Appl Neurobiol. 1980;6:361–74.
35. Lee SM, Bressler R. Prevention of diabetic nephropathy by diet control in the db/db mouse. Diabetes. 1981;30:106–11.
36. Cameiro FS, Fiachini FR, Lima VV, Cameiro ZN, Leite R, Inscho EW, Tostes RC, Webb RC. Adenosine actions are preserved in corpus cavernosum from obese and type II diabetic db/db mouse. J Sex Med. 2008;5:1156–66.
37. Kolavennu V, Zeng L, Peng H, Wang Y, Danesh FR. Targeting of RhoA/ROCK signaling ameliorates progression of diabetic nephropathy independent of glucose control. Diabetes. 2008;57:714–23.
38. Luttrell IP, Swee M, Starcher B, Parks WC, Chitaley K. Erectile dysfunction in the type II diabetic db/db mouse: impaired venoocclusion with altered cavernosal vasoreactivity and matrix. Am J Physiol Heart Circ Physiol. 2008;294:H2204–11.
39. Tompkins JD, Vizzard MA, Parsons RL. Synaptic transmission at parasympathetic neurons of the major pelvic ganglion from normal and diabetic male mice. J Neurophysiol. 2013;109:988–95.
40. Van Zwieten PA, Kam KL, Pijl AJ, Hendriks MG, Beenen OH, Pfaffendorf M. Hypertensive diabetic rats in pharmacological studies. Pharmacol Res. 1996;33:95–105.
41. Schaffer SW. Cardiomyopathy associated with noninsulin-dependent diabetes. Mol Cell Biochem. 1991;107:1–20.
42. Davidson EP, Coppey LJ, Holmes A, Lupachyk S, Dake BL, Oltman CL, Peterson RG, Yorek MA. Characterization of diabetic neuropathy in the Zucker diabetic Sprague-Dawley rat: a new animal model for type 2 diabetes. J Diabetes Res. 2014;2014:Article ID 714273.
43. Coppey LJ, Gellett JS, Davidson EP, Dunlap JA, Yorek MA. Changes in endoneurial blood flood, motor nerve conduction velocity and vascular relaxation of epineurial arterioles of the sciatic nerve in ZDF-obese diabetic rats. Diabetes Metab Res Rev. 2002;18:49–56.
44. Oltman CL, Coppey LJ, Gellett JS, Davidson EP, Lund DD, Yorek MA. Progression of vascular and neural dysfunction in sciatic nerves of Zucker diabetic fatty and Zucker rats. Am J Physiol Endocrinol Metab. 2005;289:E113–22.
45. Reinwald S, Peterson RG, Allen MR, Burr DB. Skeletal changes associated with the onset of type 2 diabetes in the ZDF and ZDSD rodent models. Am J Physiol Endocrinol Metab. 2009; 296:E765–74.
46. Davis JE, Cain J, Banz WJ, Peterson RG. Age-related differences in response to high-fat feeding on adipose tissue and metabolic profile in ZDSD rats. ISRN Obes. 2013;2013:Article ID 584547.
47. Beltowski J. Leptin and the regulation of endothelial function in physiological and pathological conditions. Clin Exp Pharmacol Physiol. 2012;39: 168–78.
48. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014;2014:Article ID 943162.
49. Ricci R, Bevilacqua F. The potential role of leptin and adiponectin in obesity: a comparative review. Vet J. 2012;191:292–8.
50. Duvnjak L, Duvnjak M. The metabolic syndrome – an ongoing story. J Physiol Pharmacol. 2009; 60:19–24.

51. Gade W, Schmit J, Collins M, Gade J. Beyond obesity: the diagnosis and pathophysiology of metabolic syndrome. Clin Lab Sci. 2010;23:51–65.
52. Burn JH, Lewis TH, Kelsey FD. The dietary control of alloxan diabetes in rats. Br Med J. 1944;9:752.
53. Musicki B, Kramer MF, Becker RE, Burnett AL. Inactivation of phosphorylated endothelial nitric oxide synthase (Ser-1177) by O-GlcNAc in diabetes-associated erectile dysfunction. Proc Natl Acad Sci U S A. 2005;102:11870–5.
54. Preston GM. Peripheral neuropathy in the alloxan-diabetic rat. J Physiol. 1967;189:49P–50.
55. Marini P, Vitadello M, Bianchi R, Triban C, Gorio A. Impaired axonal transport of acetylcholinesterase in the sciatic nerve of alloxan-diabetic rats: effect of ganglioside treatment. Diabetologia. 1986;29: 254–8.
56. Khomulo PS, Khegal MD. Adrenal cortex function and development of vascular changes in rabbits with alloxan diabetes. Probl Endokrinol (Mosk). 1977;23:97–9.
57. McNeil JH. 1983 Upjohn award lecture. Endocrine dysfunction and cardiac performance. Can J Physiol Pharmacol. 1985;63:1–8.
58. Thompson EW. Structural manifestations of diabetic cardiomyopathy in the rat and its reversal by insulin treatment. Am J Anat. 1988;182:270–82.
59. Chang S, Hypolite JA, Changolkar A, Wein AJ, Chacko S, Di Santo ME. Increased contractility of diabetic rabbit corpora smooth muscle in response to endothelin is mediated via Rho-kinase β. Int J Impot Res. 2003;15:53–62.
60. Akingba AG, Burnett AL. Endothelial nitric oxide synthase protein expression, localization, and activity in the penis of the alloxan-induced diabetic rat. Mol Urol. 2001;5:189–97.
61. Ishida K, Mizuno A, Min Z, Sano T, Shima K. Which is the primary etiologic event in Otsuka Long-Evans Tokushima fatty rats, a model of spontaneous non-insulin-dependent diabetes mellitus, insulin resistance, or impaired insulin secretion? Metabolism. 1995;44:940–5.
62. Kawano K, Hirashima T, Mori S, Natori T. OLETF (Otsuka Long-Evans Tokushima fatty) rat: a new NIDDM rat strain. Diabetes Res Clin Pract. 1994;24:S317–20.
63. Nakamura J, Koh N, Sakakibara F, Hamada Y, Wakao T, Sasaki H, Mori K, Nakashima E, Naruse K, Hotta N. Diabetic neuropathy in sucrose-fed Otsuka Long-Evans Tokushima fatty rats: effect of an aldose reductase inhibitor, TAT. Life Sci. 1997;60:1847–57.
64. Kamenov Z, Higashino H, Todorova M, Kajimoto N, Suzuki A. Physiological characteristics of diabetic neuropathy in sucrose-fed Otsuka Long-Evans Tokushima fatty rats. Methods Find Exp Clin Pharmacol. 2006;28:13–8.
65. Nakamura J, Jamada Y, Sakakibara F, Hara T, Wakao T, Mori K, Nakashima E, Naruse K, Kamijo M, Koh N, Hotta N. Physiological and morphometric analysis of neuropathy in sucrose-fed OLETF rats. Diabetes Res Clin Pract. 2001;51:9–20.
66. Lim YH, Joe JH, Jang KS, Song YS, So BI, Fang CH, Shin J, Kim JH, Lim HK, Kim KS. Effects of granulocyte-colony stimulating factor (G-CSF) on diabetic cardiomyopathy in Otsuka Long-Evans Tokushima fatty rats. Cardiovasc Diabetol. 2011; 10:92.
67. Kataoka T, Hotta Y, Maeda Y, Kimura K. Assessment of androgen replacement therapy for erectile function in rats with type 2 diabetes mellitus by examining nitric oxide-related and inflammatory factors. J Sex Med. 2014;11:920–9.
68. Kim SO, Lee HS, Ahn K, Park K. COMP-angiopoietin-1 promotes cavernous angiogenesis in a type 2 diabetic rat model. J Korean Med Sci. 2013;28:725–30.
69. 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.
70. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357:762–74.
71. Corona G, Lee DM, Forti G, et al. Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS),". J Sex Med. 2010;7: 1362–80.
72. Majeed SK. Survey on spontaneous peripheral neuropathy in aging rats. Arzneimittelforschung. 1992;42:986–90.
73. Kemi M, Keenan KP, McCoy C, Hoe C-M, Soper K, Ballam GC, van Zwieten MJ. The relative protective effects of moderate dietary restriction versus dietary modification on spontaneous cardiomyopathy in male Sprague-Dawley rats. Toxicol Pathol. 2000; 28:285–96.
74. Shen Z-J, Jin X-D, Chen Z-D, Shi Y-H. Effect of aging on penile ultrastructure. Asian J Androl. 2001;3:281–4.
75. Yamanaka M, SHirai M, Shiina H, Shirai M, Tanaka Y, Fujime M, Okuyama A, Dahiya R. Loss of anti-apoptotic genes in aging rat crura. J Urol. 2002;168:2296–300.
76. Shi JP, Zhao YM, Song YT. Effect of aging on expression of nitric oxide synthase I and activity of nitric oxide synthase in rat penis. Asian J Androl. 2003;5:117–20.
77. Gurenewald DA, Naai MA, Hess DL, Matsumoto AM. The brown Norway rat as a model of male reproductive aging: evidence for both primary and secondary testicular failure. J Gerentol. 1994; 49:B42–50.
78. Gurenewald DA, Hess DL, Wilkinson CW, Matsumoto AM. Excessive testicular progesterone secretion in aged male Fischer 344 rats: a potential

cause of age-related gonadotropin suppression and confounding variable in aging studies. J Gerentol. 1992;47:B164–70.
79. Davila HH, Rajfer J, Gonzalez-Cadavid NF. Corporal veno-occlusive dysfunction in aging rats: evaluation by cavernosometry and cavernosography. Urology. 2004;64:1261–6.
80. Moody JA, Vernet D, Laidlaw S, Rajfer J, Gonzalez-Cadavid NF. Effects of long-term oral administration of L-arginine on the rat erectile response. J Urol. 1997;158:942–7.
81. Garban H, Marquez D, Cai L, Rajfer J, Gonzalez-Cadavid NF. Restoration of normal adult penile erectile response in aged rats by long-term treatment with androgens. Biol Reprod. 1995;53:1365–72.
82. Ferrini MG, Kovanecz I, Sanchex S, Vernet D, Davila HH, Rajfer J, Gonzalez-Cdavid NF. Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat. Biol Reprod. 2007;76:915–23.
83. Thomas PK, King RH, Sharma AK. Changes with age in the peripheral nerves of the rat. An ultrastructural study. Acta Neuropathol. 1980;52:1–6.
84. Wang YJ, Zhou CJ, Shi Q, Smith N, Li TF. Aging delays the regeneration process following sciatic nerve injury in rats. J Neurotrauma. 2007;24: 885–94.
85. Lin JS, Tsai Y-S, Lin Y-M, Lin C-S, Chow N-H. Age-associated changes in collagen content and its subtypes within rat corpora cavernosa with computerized histomorphometric analysis. Urology. 2001;57: 837–42.
86. Costa C, Vendeira P. Does erectile tissue angioarchitecture modify with aging? An immunohistological and morphometric approach. J Sex Med. 2008;5: 833–40.
87. Ferrini MG, Davila HH, Valente EG, Gonzalez-Cadavid NF, Rajfer J. Aging-related induction of inducible nitric oxide synthase is vasculo-protective to the arterial media. Cardiovasc Res. 2004;61: 796–805.
88. Mallidis C, Czerwiec A, Filippi S, O'Neill J, Maggi M, McClure N. Spermatogenic and sperm quality differences in an experimental model of metabolic syndrome and hypogonadal hypogonadism. Reproduction. 2011;142:63–71.
89. Wingard CJ, Moukdar F, Prasad RY, Cathey BL, Wilkinson L. Reversal of voltage-dependent erectile responses in the Zucker obese-diabetic rat by rosuvastatin-altered RhoA/Rho-kinase signaling. J Sex Med. 2009;6:269–78.
90. Wingard C, Fulton D, Husain S. Altered penile vascular reactivity and erection in the Zucker obese-diabetic rat. J Sex Med. 2007;4:362–3.
91. Contreras C, Sanchez A, Martinez P, Raposo R, Climent B, Garcia-Sacristan A, Benedito S, Prieto D. Insulin resistance in penile arteries from a rat model of metabolic syndrome. Br J Pharmacol. 2010;161:350–64.
92. Liu Z-H, Yu L-P, Xu T, Zhang X-W, Yuan Y-Q, Xiao Y-B, Li J, Hao Y-C, Zhao Y-P, Wang X-F. Abnormal lipid metabolism down-regulates adenosine triphosphate synthase β-subunit protein expression in corpus cavernosum smooth muscle in vitro and in vivo. Andrologia. 2014;46:487–94.
93. Nangle MR, Proietto J, Keast JR. Impaired cavernous reinnervation after penile nerve injury in rats with features of the metabolic syndrome. J Sex Med. 2009;6:3032–44.
94. Jensen J, Lendorf A, Stimpel H, Frost J, Ibsen H, Rosenkilde P. The prevalence and etiology of impotence in 101 male hypertensive outpatients. Am J Hypertens. 1999;12:271–5.
95. Lewis RW, Hatzichriston DG, Laumann E, McKinlay JB. Epidemiology and natural history of erectile dysfunction: risk factors including iatrogenic and aging. In: Jardin A, Wagner AH, Khoury S, Giuliano F, Padma-Nathan II, Rosen M, editors. Proceedings of the first international consultation on erectile dysfunction. Plymouth: Health Publication; 2000. p. 21–51.
96. Behr-Roussel D, Gorny D, Mevel K, Compagnie S, Kern P, Sivan V, Bernabe J, Bedigian MP, Alexandre L, Giuliano F. Erectile dysfunction: an early marker for hypertension? A longitudinal study in spontaneously hypertensive rats. Am J Physiol Integr Comp Physiol. 2005;288:R276–83.
97. Mao JB, Xu CX, Jiang R. Expressions of phosphor-Erk1/2 and phosphor-Akt1 in the corpus cavernosum of spontaneous hypertensive rats. Zhonghua Nan Ke Xue. 2010;16:24–8.
98. Yono M, Yamamoto Y, Yoshida M, Ueda S, Latifpour J. Effects of doxazosin on blood flow and mRNA expression of nitric oxide synthase in the spontaneously hypertensive rat genitourinary tract. Life Sci. 2007;81:218–22.
99. Toblli JE, Stella I, Inserra F, Ferder L, Zeller F, Mazza ON. Morphological changes in cavernous tissue in spontaneously hypertensive rats. Am J Hypertens. 2000;13:686–92.
100. Jiang YG, Jiang R, Jin J, Wang HP, Chen JH. Changes of gap junction in penile cavernous smooth muscle cells of hypertensive rats. Zhonghua Nan Ke Xue. 2006;12:1010–3.
101. Toblli JE, Cao G, Lombrana A, Rivero M. Functional and morphological improvement in erectile tissue of hypertensive rats by long-term combined therapy with phosphodiesterase type 5 inhibitor and losartan. J Sex Med. 2007;4:1291–303.
102. Mazza ON, Angerosa M, Becher E, Toblli JE. Differences between Candesartan and Hydralazine in the protection of penile structures in spontaneously hypertensive rats. J Sex Med. 2006;3:604–11.
103. Labazi H, Wynne BM, Tostes R, Webb RC. Metformin treatment improves erectile function

in an angiotensin II model of erectile dysfunction. J Sex Med. 2013;10:2154–64.
104. Xie Y, Garban H, Ng C, Rajfer J, Gonzalez-Cadavid NF. Effect of long-term passive smoking on erectile function and penile nitric oxide synthase in the rat. J Urol. 1997;157:1121–6.
105. Roumeguere T, Wespes E, Carpentier Y, Hoffmann P, Schulman CC. Erectile dysfunction is associated with a high prevalence of hyperlipidemia and coronary heart disease risk. Eur Urol. 2003;44:355–9.
106. Wei M, Macera CA, Davis DR, Hornung CA, Nankin HR, Blair SN. Total cholesterol and high density lipoprotein cholesterol s important predictors of erectile dysfunction. Am J Epidemiol. 1994;140:930–7.
107. Yang G, Chen Z, Wang H. Establishment of the animal model of induced high-cholesterol-atherosclerotic erectile dysfunction and the mechanisms of atherosclerotic erectile dysfunction. Zhonghua Nan Ke Xue. 2004;10:608–11.
108. Xie D, Kontos CD, Donatucci CF, Annex BH. Cholesterol feeding reduces vascular endothelial growth factor signaling in rabbit corporal tissues. J Sex Med. 2005;2:634–40.
109. Rahman NU, Phonsombat S, Bochinski D, Carrion RE, Nunes L, Lue TF. An animal model to study lower urinary tract symptoms and erectile dysfunction: the hyperlipidaemic rat. BLU Int. 2007;100: 658–63.
110. Huang YC, Ning H, SHindel AW, Fandel TM, Lin G, Harraz AM, Lue TF, Lin CS. The effect of intracavernous injection of adipose tissue-derived stem cells on hyperlipidemia-associated erectile dysfunction in a rat model. J Sex Med. 2010;7:1391–400.
111. Folkow B, Hallback M, Lundgren Y, Sivertsson R, Weiss L. Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and in spontaneously hypertensive rats. Circ Res. 1973;32 Suppl 1:2–16.
112. Plump AS, Smith JD, Hayek T, Aalto-Setala K, Walsh A, Verstuyft JG, Rubin EM, Breslow JL. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell. 1992; 71:343–53.
113. D'Uscio LV, Barton M, Shaw S, Luscher TF. Chronic ET(A) receptor blockade prevents endothelial dysfunction of small arteries in apolipoprotein E-deficient mice. Cardiovasc Res. 2002;53:487–95.
114. Gervais M, Pons S, Nicoletti A, Cosson C, Giudicelli JF, Richer C. Fluvastatin prevents renal dysfunction and vascular NO deficit in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2003;23: 183–9.
115. Jiang F, Gibson AP, Dusting GJ. Endothelial dysfunction induced by oxidized low-density lipoproteins in isolated mouse aortal A comparison with apolipoprotein-E deficient mice. Eur J Pharmacol. 2001;424:141–9.
116. Seo HS, Lombardi DM, Polinsky P, Powell-Braxton L, Bunting S, Schwartz SM, Rosenfeld ME. Peripheral vascular stenosis in apolipoprotein E-deficient mice. Potential roles of lipid deposition, medial atrophy, and adventitial inflammation. Arterioscler Thromb Vasc Biol. 1997;17:3593–601.
117. Nakashima Y, Plump AS, Raines EW, Breslow JL, Ross R. ApoE-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree. Arterioscler Thromb. 1994;14:133–40.
118. Barton M, Haudenschild CC, d'Uscio LV, Shaw S, Munter K, Luscher TF. Endothelin ETA receptor blockade restores NO-mediated endothelial function and inhibits atherosclerosis in apolipoprotein E-deficient mice. Proc Natl Acad Sci U S A. 1998; 95:14367–72.
119. D'Uscio LV, Baker TA, Mantilla CB, Smith L, Weiler D, Sieck GC, Katusic ZS. Mechanism of endothelial dysfunction in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2001;21: 1017–22.
120. Raij L, Hayakawa H, Coffee K, Guerra J. Effect of doxazosin on endothelial dysfunction in hypercholesterolemic/antioxidant-deficient rats. Am J Hypertens. 1997;10:1257–62.
121. Behr-Roussel D, Darblade B, Oudot A, Compagnie S, Bernabe J, Alexandre L, Giuliano F. Erectile dysfunction in hypercholesterolemic atherosclerotic apolipoprotein E knockout mice. J Sex Med. 2006;3:596–603.
122. Xie D, Odronic SI, Wu F, Pippen AM, Donatucci CF, Annex BH. A mouse model of hypercholesterolemia-induced erectile dysfunction. J Sex Med. 2007;4:898–907.
123. De Young L, Bella A, Howard J, Brock G. Arteriogenic erectile dysfunction alters protein expression within the cavernosal tissue in an animal model. J Sex Med. 2005;2:199–206.
124. Gonzalez-Cadavid NF. Mechanisms of penile fibrosis. J Sex Med. 2009;3:353–62.
125. Shiota A, Hotta Y, Kataoka T, Morita M, Maeda Y, Kimura K. Oral L-citrulline supplementation improves erectile function in rats with acute arteriogenic erectile dysfunction. J Sex Med. 2013;10:2423–9.
126. El-Sakka A, Yen TS, Lin CS, Lue TF. Traumatic arteriogenic erectile dysfunction a rat model. Int J Impot Res. 2001;13:162–71.
127. Hotta Y, Hattori M, Kataoka T, Ohno R, Mikumo M, Maeda Y, Kimura K. Chronic vardenafil treatment improves erectile function via structural maintenance of penile corpora cavernosa in rats with acute arteriogenic erectile dysfunction. J Sex Med. 2011;8:705–11.
128. Vignozzi L, Filippi S, Morelli A, AMbrosini S, Luconi M, Vannelli GB, Donati S, Crescioli C, Zhang XH, Mirone V, Forti G, Maggi M. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. J Sex Med. 2006;3:419–31.

129. Vignozzi L, Filippi S, Morelli A, Marini M, CHavalmane A, Fibbi B, Silvestrini E, Mancina R, Carini M, Vannelli GB, Forti G, Maggi M. Cavernous neurotomy in the rat is associated with the onset of an overt condition of hypogonadism. J Sex Med. 2009;6:1270–83.
130. Yuan J, Westney OL, Ruan KH, Wang R. A new strategy, SuperEnzyme gene therapy in penile rehabilitation. J Sex Med. 2009;6 Suppl 3:328–33.
131. Yuan J, Lin H, Li P, Zhang R, Luo A, Berardinelli F, Dai Y, Wang R. Molecular mechanisms of vacuum therapy in penile rehabilitation: a novel animal study. Eur Urol. 2010;58:773–80.
132. Lee CH, Kim HS, Goo MJ, Kang KK, Ahn BO, Kim SH, Yang DY. Chronic administration of udenafil, a selective phosphodiesterase type 5 inhibitor, promotes erectile function recovery in an animal model of bilateral cavernous nerve crush injury. J Sex Med. 2011;8:1330–40.
133. Ryu JK, Lee M, Choi MJ, Kim HA, Jin HR, Kim WJ, Yin GN, Song KM, Kwon MH, Suh JK. Gene therapy with an erythropoietin enhancer-mediated, hypoxia-inducible gene expression system in the corpus cavernosum of mice with high-cholesterol diet-induced erectile dysfunction. J Androl. 2012;33:845–53.
134. Tar MT, Martinez LR, Nosanchuk JD, Davies KP. The effect of methamphetamine on an animal model of erectile function. Andrology. 2014; 2:531–6.
135. Incrocci L. Sexual function after external-beam radiotherapy for prostate cancer: what do we know? Crit Rev Oncol Hematol. 2006;57:165–73.
136. Teloken PE, Parker M, Mohideen N, Mulhall JP. Predictors of response to sildenafil citrate following radiation therapy for prostate cancer. J Sex Med. 2009;6:1135–40.
137. Goldstein I, Feldman MI, Deckers PJ, Babayan RK, Krane RJ. Radiation-associated impotence. A clinical study of its mechanism. JAMA. 1984;251:903–10.
138. Mulhall J, Ahmed A, Parker M, Mohideen N. The hemodynamics of erectile dysfunction following external beam radiation for prostate cancer. J Sex Med. 2005;2:432–7.
139. Zelefsky MJ, Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostatic cancer. Int J Radiat Oncol Biol Phys. 1998;40:129–33.
140. Koontz BF, Kimura M, Vujaskovic Z, Donatucci C, Yin F-F. Feasibility study of an intensity-modulated radiation model for the study of erectile dysfunction. J Sex Med. 2011;8:411–8.
141. Kimura M, Rabbani ZN, Zodda AR, Yan H, Jackson IL, Polascik TJ, Donatucci CF, Moul JW, Vujaskovic Z, Koontz BF. Role of oxidative stress in a rat model of radiation-induced erectile dysfunction. J Sex Med. 2012;9:1535–49.
142. Qiu X, Villalta J, Ferretti L, Fandel TM, Albersen M, Lin G, Dai Y, Lue TF, Lin CS. Effects of intravenous injection of adipose-derived stem cells in a rat model of radiation therapy-induced erectile dysfunction. J Sex Med. 2012;9:1834–41.
143. Carrier S, Hricak H, Lee SS, Baba K, Morgan DM, Nunes L, Ross GY, Phillips TL, Lue TF. Radiation-induced decrease n nitric oxide synthase-containing nerves in the rat penis. Radiology. 1995; 195:95–9.
144. Kimura M, Yan H, Rabbani Z, Satoh T, Baba S, Yin FF, Polascik TJ, Donatucci CF, Vujaskovic Z, Koontz BF. Radiation-induced erectile dysfunction using prostate-confined modern radiotherapy in a rat model. J Sex Med. 2011;8:2215–26.
145. Takane KK, George FW, Wilson JD. Androgen receptor of rat penis is downregulated by androgen. Am J Physiol. 1990;258:E46–50.
146. Podlasek CA, Zelner DJ, Jiang HB, Tang Y, Houston J, McKenna KE, McVary KT. Sonic hedgehog cascade is required for penile postnatal morphogenesis, differentiation, and adult homeostasis. Biol Reprod. 2003;68:423–38.

Normal Erectile Physiology

2

Gregory B. Auffenberg, Joseph J. Pariser, and Brian T. Helfand

Anatomical Review

Gross Structure

The human penis is composed of the paired dorsal corpora cavernosa and the ventrally placed corpus spongiosum. The corpus spongiosum contains the urethra and is contiguous with the glans penis distally. Each corpus is surrounded by a fibrous sheath, the tunica albuginea. Between the two corpora cavernosa is an incomplete perforated septum allowing them to function in unison [1]. Surrounding all three corpora is an additional fibrous layer, Buck's fascia. Superficial to Buck's fascia is Colles' fascia extending from the base of the glans to the urogenital diaphragm where it is contiguous with Scarpa's fascia. Superficial to Colles' fascia is the skin (Fig. 2.1). Proximally, the corpora cavernosa form the penile crura, which are anchored to the pubic rami and are covered by the ischiocavernosus muscles [1]. The proximal corpus spongiosum forms the penile bulb, which is enveloped in the bulbospongiosus muscle. The suspensory ligament of the penis arises from the linea alba and pubic symphysis. It inserts on the tunica albuginea to support the pendulous portion of the penis [2].

Corpora

The corpora cavernosa are two spongy cylinders composed primarily of arterial sinusoids and smooth muscle surrounded by the tunica albuginea. The cavernosal tunica albuginea is 2–3 mm thick in the flaccid state and is composed mostly of collagen fibers with a smaller portion being elastic fibers [3]. The tunica of the cavernosa has an inner circular layer and an outer longitudinal layer of fibers [1].

The histologic appearance of corpus spongiosum is similar to the corpora cavernosa and it contains larger sinusoids. Additionally, the tunica albuginea surrounding this corpus is thinner, has only one circular fiber layer, and contains more elastic fibers [3].

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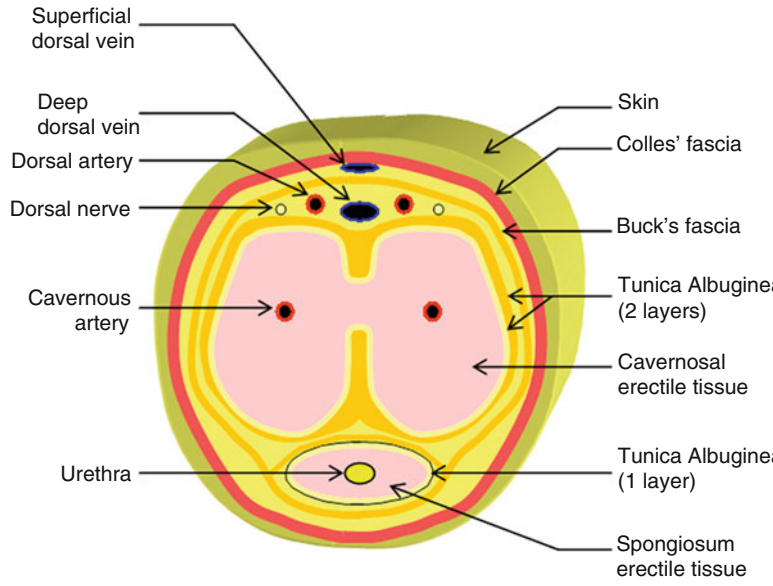

Fig. 2.1 Penile cross section. Penile cross section showing paired dorsal corpora cavernosa and the ventral corpus spongiosum. Note the double-layered tunica albuginea surrounding the cavernosa (inner circular and outer longitudinal) and the incomplete septum allowing communication of the two cavernosa. Note urethra coursing within the corpus spongiosum and the single-layered tunica (one circular layer)

Glans

The glans forms the distal portion of the penis. It is contiguous with the corpus spongiosum. It is covered with very thin but firmly adherent skin. Additionally, the tunica on the glans [1] albuginea is absent.

Arterial Supply

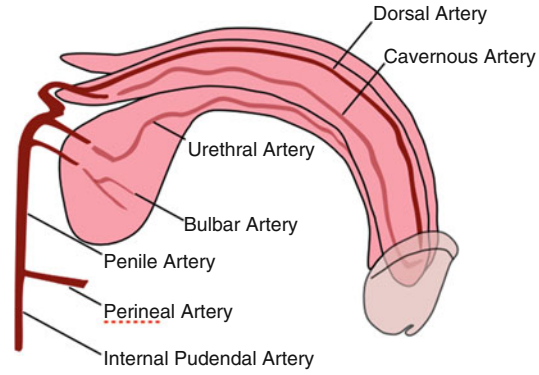

Fig. 2.2 Arterial supply to the penis. The internal pudendal artery forms the penile artery after giving off the perineal artery. The penile artery has four terminal branches: the bulbar, urethral, cavernous, and dorsal artery. Penile blood supply is bilaterally symmetric; only one side of supply is portrayed in this diagram

Classically, the internal pudendal artery, which is a branch of the internal iliac, serves as the main blood supply to the penis [1]. After the perineal artery branch, it becomes the penile artery. More recently, accessory pudendal arteries, arising from the external iliac, obturator, vesical, and femoral arteries, have been shown to contribute to the blood supply of the penile artery in many men [4]. The penile artery has four paired terminal branches: the cavernous (deep penile), dorsal, urethral, and bulbar arteries [1, 5] (Fig. 2.2). Each cavernous artery pierces the ipsilateral cavernosal tunica albuginea at the hilum of the penis and enters the penile crura. It runs the length of the corpora cavernosa giving off many tortuous branches, which are known as the helicine arteries. These helicine arteries open directly into the sinusoids of the erectile tissue. Each dorsal artery lies beneath Buck's fascia and courses distally between the laterally placed paired dorsal nerves and the deep dorsal vein. They are responsible for the engorgement of the glans during erection. The urethral arteries run through the corpus spongiosum lateral to the urethra and supply blood to the corpus spongiosum, the urethra, and the

glans. The bulbar arteries enter the bulb of the penis supplying the proximal urethra and Cowper's gland.

Veins

Within the three corpora, tiny post-cavernous venules coalesce to form emissary veins that continue further and ultimately pierce the tunica albuginea [6]. In the proximal penis, the emissary veins drain into the cavernous vein that goes on to join the periurethral veins of the urethral bulb to form the internal pudendal vein. The emissary veins from the distal and middle penis combine to form circumflex veins, which drain into the deep dorsal vein of the penis. The deep dorsal vein runs the length of the dorsal penis and drains into the periprostatic plexus. The venous drainage of the skin and subcutaneous penile tissue is via multiple superficial veins that go on to form the superficial dorsal vein. This vein drains into the external pudendal vein.

Peripheral Innervation

The penis receives innervation from parasympathetic, sympathetic, and somatic efferent nerves (Fig. 2.3). The parasympathetic penile innervation comprises the major excitatory input to the penis responsible for vasodilation of the penile vasculature and erection. Preganglionic fibers originate from the sacral parasympathetic nucleus [4, 7]. These fibers travel to the pelvic plexus via the pelvic nerve, which also carries sympathetic nerve fibers [7, 8]. After synapsing in the pelvic plexus, postganglionic parasympathetic fibers emerge as a part of the cavernous nerve [9]. The cavernous nerve travels along the posterolateral

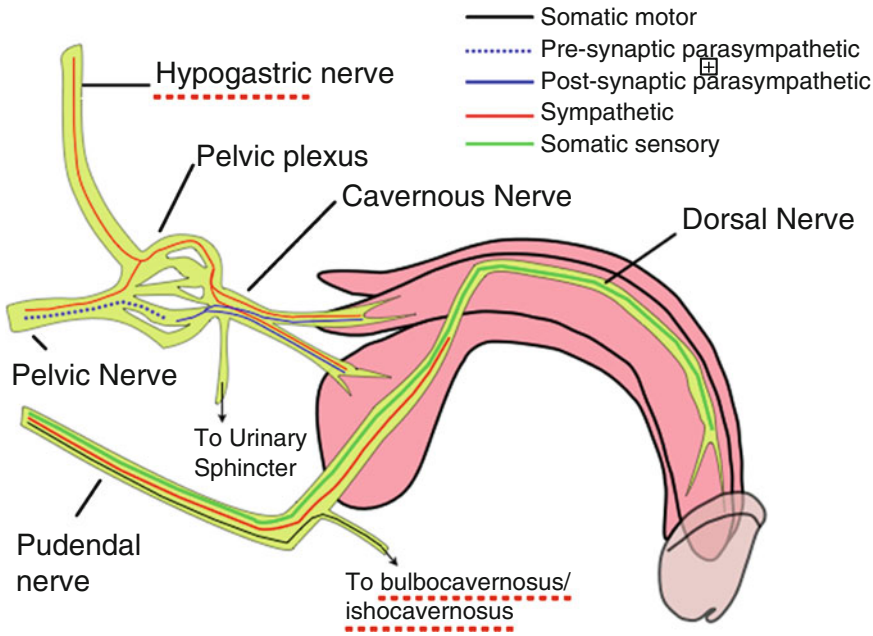

Fig. 2.3 Innervation of the penis. Presynaptic parasympathetic fibers travel via pelvic nerve to synapse in pelvic plexus; postsynaptic fibers emerge within cavernous nerve and travel to corporal bodies as well as urinary sphincter. Sympathetic fibers travel via hypogastric and pelvic nerves to join cavernous nerve as it emerges from the pelvic plexus. Sympathetic fibers also travel to penis via pudendal nerve. Somatic motor fibers to the bulbocavernosus and ischiocavernosus travel via pudendal nerve. Somatic sensory afferent signals travel from the penis via the dorsal nerve which goes on to join the pudendal nerve

aspect of the prostate within the pelvic fascia that fuses with the prostatic capsule [10]. The cavernous nerves then exit the pelvis as two groups of fibers [10]. The first group travels to the urethral sphincter to modify urinary function. The second group travels to the penis. This group branches further as it reaches the penis with a portion of the fibers heading for the corpus spongiosum and the remaining fibers entering the penile crura along with the deep penile artery and cavernous veins [10].

Sympathetic pathways begin in the intermediolateral cell column and intercalated nucleus at spinal levels T9-L2 [8, 11]. Preganglionic fibers emerge and travel to synapse on sacral and caudal lumbar ganglion cells within the sympathetic chain [12]. Postganglionic sympathetic nerve fibers that innervate the penis exit the sympathetic chain via three routes. The first carries sympathetic fibers via the hypogastric nerve to the pelvic plexus where they join the cavernous nerve for the remaining distance to the penis. In the second pathway, postsynaptic sympathetic outflow from paravertebral ganglia joins the pelvic nerve, which travels to the pelvic plexus to join the cavernous nerve to the penis. Finally, a portion of the sympathetic outflow is carried on a direct route to the penis from the sympathetic chain ganglia via the pudendal nerve [9]. The role of these sympathetic neurons appears to be primarily one of antierectile function. They stimulate vasoconstriction and appear to have spontaneous activity that produces an antierectile tone [9, 13]. However, total eradication of sympathetic input leads to diminished erectile function demonstrating that the sympathetic input is not entirely antierectile [9, 11, 14]. Opinions differ on the reason for this effect as some authors have suggested that due to the vital role of sympathetic input for arterial tone and regulation of blood distribution, a sympathetic lesion may disrupt routing of blood to the penis [14].

Somatic motor efferents arise from the ventral sacral spinal cord (Onuf's nucleus). They travel via the pudendal nerve to innervate the bulbospongiosus and ischiocavernosus muscles [9]. Neural input to these muscles in the presence of an erect penis leads to increased penile rigidity [15]. Additionally, contraction of these muscles in a rhythmic manner assists in the expulsion of ejaculate [9].

Somatosensory input from the penis arises primarily at free nerve endings and corpuscular receptors. The input is carried via C- and A-delta fibers [16]. These fibers coalesce to form the dorsal nerve of the penis, which extends into the pelvis to join the pudendal nerve. The pudendal nerve carries sensory signals to the spinal cord via spinal roots S2–S4 and terminates in the gray matter of the lumbosacral cord [17].

Hemodynamics of Erection

Flaccid State

The flaccid state of the penis is characterized by blood flow sufficient to meet nutritional and other physiologic needs, but insufficient for penile erection. During this state, sustained partial contraction of smooth muscle cells in the walls of arteries, arterioles, and in the corporal trabeculae is essential for the limitation of blood flow. The molecular mechanisms leading to this tonic smooth muscle contraction are discussed below.

Tumescence and Erection

With sexual stimulation and subsequent release of proerectile mediators onto corporal smooth muscle the erectile response is initiated. Within the corpora cavernosa, there is dilation of arteries and arterioles and thus increased inflowing blood. The trabecular smooth muscle additionally relaxes allowing corporal sinusoids to expand as they become engorged with blood. This cavernosal expansion begins to compress the subtunical venules decreasing venous outflow. With further engorgement, the tunica is stretched occluding the emissary veins between the two tunical layers leading to minimal venous outflow [18]. This leads to an increase in intracavernosal pressure to approximately 100 mmHg, which raises the penis to the fully erect position [18].

During heightened sexual activity, the penis enters the rigid-erection phase. The ischiocaver-

nosus muscles contract as a result of the bulbocavernosus reflex, compressing the base of the corpora cavernosa leading to temporary cessation of inflow and outflow of blood and increasing intracavernous pressures up to several hundred mmHg [18].

The corpus spongiosum and glans behave somewhat differently in tumescence and erection. Arterial flow increases in these locations just as in the cavernosa. Due to structural differences in the tunica albuginea, which is thin in the spongiosum and absent in the glans, venous occlusion is less in these locations. This leads to pressures in the spongiosum only one third to one half of that of the cavernosa [19]. The glans and spongiosum thus act essentially as arteriovenous shunts during erection. Similar to the corpora cavernosa, during the rigid-erection phase contraction of the ischiocavernosus and bulbocavernosus muscles compresses out-flowing veins leading to further pressure increase in the spongiosum and glans. The deep dorsal vein is compressed between the engorged cavernosa and Buck's fascia contributing to rigidity of the glans [18].

Detumescence

With cessation of sexual stimulus and subsequent decrease in erection inducing neural activity, the erectile response ends. Antierectile neural input leads to vasoconstriction of penile arteries and contraction of the trabecular smooth muscle resulting in reduced arterial inflow and collapse of the trabeculae [20]. With decreased arterial inflow and subsequent corporal decompression, occlusion of venous drainage subsides, allowing efflux of corporal blood and return to flaccid state physiology [21].

Local Mechanisms of Erection

As previously mentioned, partial contraction of trabecular, arterial, and arteriolar smooth muscle and subsequent limitation of blood flow are essential for maintaining penile flaccidity. Sympathetic adrenergic signaling and the activity of substances derived from vascular endothelium (endothelins and prostaglandin $F_{2\alpha}$) appear to play a crucial role in this process [22, 23]. These substances activate G-protein-coupled receptors that initiate a cascade leading to the increased production of inositol triphosphate and diacylglycerol. In turn, these substances lead to an increase in intracellular Ca^{2+} via releasing intracellular stores or opening cell membrane channels to allow influx [19, 23, 24]. The resultant elevated intracellular free Ca^{2+} binds to calmodulin, changing its conformation to expose sites that bind and activate myosin light-chain kinase [19]. The activated myosin light-chain kinase phosphorylates myosin light chains, allowing them to initiate smooth muscle contraction [25].

This rise in intracellular Ca^{2+} is only a transient event, and further mechanisms, most notably calcium sensitization, appear to play a significant role in maintaining contraction of smooth muscle during the flaccid state. The RhoA, Rho-kinase pathway is important to calcium sensitization [26, 27]. G proteins expressed in penile smooth muscle activate RhoA which activates Rho-kinase. Rho-kinase, in turn, phosphorylates the regulatory subunit of smooth muscle myosin phosphatase, inhibiting its activity. This inhibition prevents dephosphorylation of smooth muscle myofilaments allowing them to maintain their contractile tone [28, 29]. The sum total of this pathway is the maintenance of smooth muscle contraction during the flaccid state without a significant change in intracellular Ca^{2+} [29]. RhoA is expressed at a 17-fold higher concentration in rabbit cavernosal smooth muscle when compared to other vascular smooth muscle sites supporting its important role in erectile physiology [30].

During the erectile response, a drop in intracellular Ca^{2+} is important for the relaxation of vascular and corporal smooth muscle. The release of nitric oxide (NO) from nonadrenergic, noncholinergic nerve terminals and the endothelium is a major mediator of this response [31, 32]. NO works in the smooth muscle cell to activate a soluble guanylyl cyclase. This enzyme leads to an increase in the production of the second messenger cyclic guanosine monophosphate (cGMP).

Increased cGMP concentration activates protein kinase G (PKG). The activated PKG phosphorylates multiple intracellular proteins to cause: sequestration of intracellular Ca^{2+} in the endoplasmic reticulum, inhibition of cell membrane calcium influx channels, and opening of potassium channels with resultant myocyte hyperpolarization [18]. The resultant decrease in intracellular calcium concentration and hyperpolarization leads to smooth muscle relaxation via what is essentially a reversal of the process for smooth muscle contraction described above. In brief, intracellular calcium levels fall, deactivating the calcium–calmodulin complex. This allows myosin light-chain kinase to become inactive, facilitating resultant dephosphorylation of the myosin light chains deeming them unable to initiate muscle contraction (Fig. 2.4).

During the return to flaccid state physiology, phosphodiesterase type 5 (PDE-5) hydrolyzes cGMP to the inactive guanosine monophosphate. As cGMP concentration falls, intracellular $[Ca^{2+}]$ rises and the vascular and corporal smooth muscle cells again contract [31].

These local vasodilatory mechanisms of erection represent one of the primary therapeutic targets of erectile dysfunction. The PDE-5 inhibitors block the degradation of cGMP, which leads to downstream smooth muscle relaxation. A variety of oral PDE-5 inhibitors are available for use. In general, they have similar efficacy but vary in terms of pharmacokinetics and side effect profiles.

Spinal Control of Erection

Erection can originate from both tactile stimulation of the penis (reflexive erection) and supraspinal stimuli (psychogenic erection). The sacral spinal cord appears to integrate and coordinate the excitatory and inhibitory neural inputs from both peripheral and supraspinal sources. Complete destruction of the sacral spinal cord or its outflow eliminates erectile function [33, 34]. However, patients with suprasacral spinal cord transection have shown erectile function to be at least partially maintained in response to tactile stimulation of the penis [8, 33–35]. This has led to postulation that sacral centers are essential for erection regardless of origin (i.e., reflexive or psychogenic) [12]. The sacral spinal reflex, which can function in

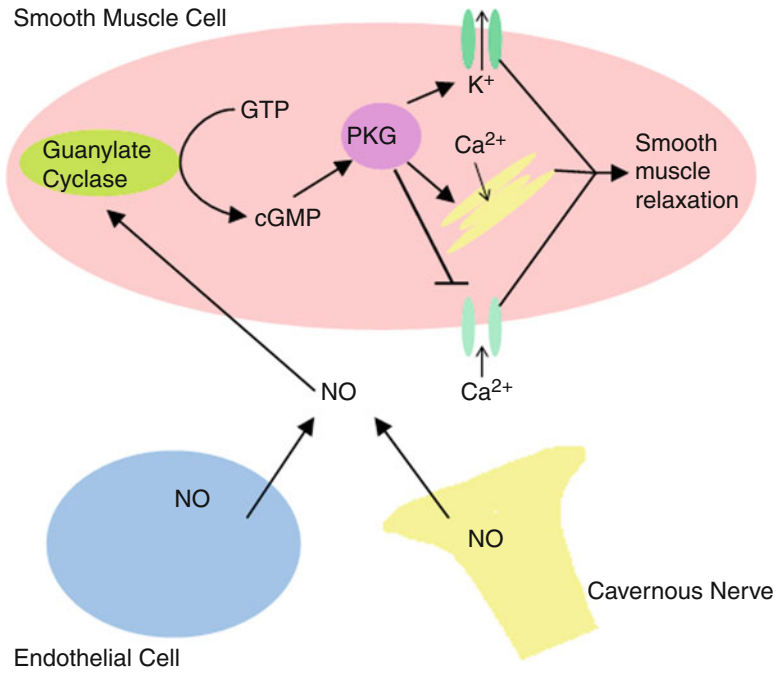

Fig. 2.4 Smooth muscle relaxation. Nitric oxide (NO) released from endothelium and cavernous nerve terminals stimulates guanylate cyclase within smooth muscle cell leading to the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). cGMP activates protein kinases (PKG) which phosphorylate proteins leading to potassium efflux, calcium sequestration in the endoplasmic reticulum, and blockage of calcium membrane channels. Calcium sequestration and hyperpolarization lead to smooth muscle cell relaxation via inactivation of myosin contractile units

the absence of suprasacral signals, coordinates sensory input from the dorsal nerve of the penis and proerectile output via sacral parasympathetics facilitating erection in response to direct penile stimulation. Additionally, sacral centers are vital to the integration of psychogenic erectile stimuli from supraspinal origins and the resultant erectile response, as evidenced by the absence of psychogenic erection in patients with sacral destruction.

Supraspinal Control of Erection

Supraspinal control of erection is poorly understood with almost all evidence from experimental animal models. Erections in response to imaginative, visual, tactile, and olfactory stimuli are thought to originate from supraspinal centers. Hypothalamic and limbic pathways have been shown to play a key role [9].

Paraventricular Nucleus

The hypothalamic paraventricular nucleus (PVN) contains premotor neurons that project from the parvocellular layer directly into the spinal cord [36–38]. These neurons have been shown to contain a variety of neurotransmitters: oxytocin, vasopressin, enkephalins, and dopamine [39, 40]. In rat models injection of a variety of neuromediators (oxytocin, glutamate, nitric oxide, dopamine agonists) into the PVN has been shown to elicit penile erection [39, 40]. Additionally, in both rats and monkeys, stimulation of the PVN elicits erection [41]. Lesions of the parvocellular layer of the PVN cause longer latencies and fewer noncontact erections in rats [42]. Parvocellular PVN neurons have been shown to respond to stimulation of the dorsal nerve of the penis in rats, suggesting that the PVN may be a supraspinal reflex center for erections [43]. The PVN also receives input from the medial preoptic area (MPOA), suggesting that the PVN serves to integrate MPOA input before sending it downstream via autonomic pathways selectively activated within the PVN [9, 44].

Medial Preoptic Area

Function of the MPOA of the hypothalamus is imperative to normal sexual behavior [45, 46]. In rats and monkeys, MPOA stimulation elicits erection [41, 47]. In monkeys, increases in MPOA neuronal activity have been recorded during erection [48]. Interestingly, MPOA lesions do not affect reflexive or noncontact erections [49, 50]. All of this has led to debate as to the role of the MPOA in erectile function. The emerging theory is that the MPOA likely serves as an integration center of hormonal and sensory inputs for sexual behavior and redistributes these signals to the hypothalamic and brainstem structures thought to be more directly linked to erectile control, such as the PVN [17, 44, 51].

Other Supraspinal Centers

Many other supraspinal areas have been shown in animal studies to be related to erectile function. In monkeys, isolated stimulation of the medial dorsal nucleus of the thalamus, ventral tegmental area, precallosal cingulate gyrus, and subcallosal and caudal gyrus led to erections [41]. Hippocampal stimulation in anesthetized rats increased intracavernous pressures as did desynchronization of the somatosensory cortex following cocaine administration [52, 53]. A center for descending the inhibition of spinal sexual reflexes has been localized to a group of neurons in the paragigantocellular reticular nucleus of the ventral medulla [54]. The exact role each supraspinal area plays in mediating erection is currently unclear. However, it is apparent that there are extensive interconnections between many supraspinal centers that contribute to descending pathways and exert powerful control, both inhibitory and excitatory, on the spinal responses driving erection [51].

Central Neurotransmission

Oxytocin

Proerectile projections from the supraoptic area of the hypothalamus and the PVN travel to the spinal centers for erection and oxytocin has been shown to be a key neurotransmitter in these neurons [1, 55, 56]. In lab animals, intracerebroventricular or intrathecal injection of oxytocin antagonists blocks the induction of erection that is seen with intrathecal oxytocin injection. Additionally, antagonist injection into the lateral ventricles leads to a dose-dependant reduction in noncontact erections [57]. This has led to the belief that oxytocin plays a role in facilitating nonreflexive erections.

Dopamine

Dopaminergic neurons project to the MPOA and PVN [58] and also have been discovered to travel from the caudal hypothalamus to the lumbosacral spinal cord [59]. Dopamine is thought to participate in central regulation of the autonomic and somatic penile reflexes. The dopamine receptor agonist apomorphine induces penile erection in rats when administered systemically [60]. Additionally, apomorphine injection into the MPOA facilitated erections while dopaminergic antagonist injection into the MPOA decreased penile reflexes [60–62]. In the PVN, dopaminergic neurons appear to stimulate oxytocinergic neurons, which more directly account for the erectile response. This is supported by the prevention of apomorphine-induced erections in the presence of oxytocin receptor antagonists [63].

Serotonin

In experimental animal models, bulbospinal neurons containing serotonin (5-HT) project to the lumbar spinal cord [22]. Serotonergic fibers have been demonstrated in close proximity to retrogradely labeled sacral preganglionic neurons [64]. One study showed 5-HT in general had an inhibitory effect on male sexual behavior [65]. However, there have been conflicting reports with another study showing that the stimulation of 5-HT_{2c} receptors mediated the erectile response [66]. Thus, the full function of 5-HT in erectile function has not been fully elucidated. It appears to serve various functions likely acting as a major modulator of the central control of erection [22].

Nitric Oxide

NO is emerging as an essential neurotransmitter within the CNS for erectile response. NO appears to act in several regions of the brain, including the MPOA and PVN [67–70]. Injection of NO-synthase (NOS) inhibitors into the PVN prevents penile erection induced by dopamine agonists and oxytocin [71]. NO production increased in the PVN of rats during noncontact erections, confirming the role of NO production during erection [72].

ACTH and α-MSH

Adrenocorticotropic hormone (ACTH) and its related peptide α(alpha)-melanocyte stimulating hormone (α-MSH) have been shown to elicit erectile responses in addition to increased grooming, stretching, and yawning behaviors when given intracerebroventricularly to lab animals [73]. This proerectile effect appears to be due to the stimulation of melanocortin-3 (MC_3) receptors, which are prevalent in the hypothalamus and limbic system [74]. The role of these peptides in erectile response is not entirely known, but they appear to induce erection by acting at sites distinct from those in the PVN stimulated by dopamine and oxytocin [75]. Additionally, Melanotan II, an α-MSH synthetic analog, has been shown to have proerectile effects in humans with psychogenic impotence [76].

Other Neurotransmitters

Excitatory amino acids, such as L-glutamate, *N*-methyl-D-aspartate (NMDA), amino-3-

hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), and trans-1-amino-1,3-cyclo-pentadicarboxylic acid (ACPD), have been shown to have proerectile effects when injected into the MPOA or PVN of lab animals [77–79]. Gamma-amino butyric acid (GABA) appears to function as an inhibitor in the reflex pathways for penile erection [80]. In fact, patients with neuropathic pain who took pregabalin, a structural analog of GABA, have been shown to be at an increased risk of developing erectile dysfunction compared to untreated patients with neuropathic pain [81].

Stimulation of μ-opioid receptors appears to centrally prevent penile erection and impair copulation likely through the prevention of the increased NO production in the PVN during sexual activity [82]. Conversely, sildenafil has been shown to have anesthetic effects [83–85] and potentiate the effects of morphine [84, 85], most likely through the inhibition of cGMP degradation [85]. Clearly, further research is needed to examine the complexities of the various molecular pathways leading to physiologic erectile function along with their full extent of interactions.

References

1. Andersson KE, Wagner G. Physiology of penile erection. Physiol Rev. 1995;75(1):191–236.
2. Hoznek A, Rahmouni A, Abbou C, Delmas V, Colombel M. The suspensory ligament of the penis: an anatomic and radiologic description. Surg Radiol Anat. 1998;20(6):413–7.
3. Bitsch M, Kromann-Andersen B, Schou J, Sjontoft E. The elasticity and the tensile strength of tunica albuginea of the corpora cavernosa. J Urol. 1990;143(3):642–5.
4. Droupy S, Benoit G, Giuliano F, Jardin A. Penile arteries in humans. Origin–distribution–variations. Surg Radiol Anat. 1997;19(3):161–7.
5. Newman HF, Northup JD. Mechanism of human penile erection: an overview. Urology. 1981;17(5):399–408.
6. Hanyu S. Morphological changes in penile vessels during erection: the mechanism of obstruction of arteries and veins at the tunica albuginea in dog corpora cavernosa. Urol Int. 1988;43(4):219–24.
7. Lue TF, Takamura T, Schmidt RA, Palubinskas AJ, Tanagho EA. Hemodynamics of erection in the monkey. J Urol. 1983;130(6):1237–41.
8. Giuliano F, Rampin O, Bernabe J, Rousseau JP. Neural control of penile erection in the rat. J Auton Nerv Syst. 1995;55(1–2):36–44.
9. Giuliano F, Rampin O. Neural control of erection. Physiol Behav. 2004;83(2):189–201.
10. Lepor H, Gregerman M, Crosby R, Mostofi FK, Walsh PC. Precise localization of the autonomic nerves from the pelvic plexus to the corpora cavernosa: a detailed anatomical study of the adult male pelvis. J Urol. 1985;133(2):207–12.
11. Giuliano F, Bernabe J, Jardin A, Rousseau JP. Antierectile role of the sympathetic nervous system in rats. J Urol. 1993;150(2 Pt 1):519–24.
12. Steers WD. Neural pathways and central sites involved in penile erection: neuroanatomy and clinical implications. Neurosci Biobehav Rev. 2000;24(5):507–16.
13. Janig W, McLachlan EM. Organization of lumbar spinal outflow to distal colon and pelvic organs. Physiol Rev. 1987;67(4):1332–404.
14. Whitelaw GP, Smithwick RH. Some secondary effects of sympathectomy; with particular reference to disturbance of sexual function. N Engl J Med. 1951;245(4):121–30.
15. Schmidt MH, Schmidt HS. The ischiocavernosus and bulbospongiosus muscles in mammalian penile rigidity. Sleep. 1993;16(2):171–83.
16. Halata Z, Munger BL. The neuroanatomical basis for the protopathic sensibility of the human glans penis. Brain Res. 1986;371(2):205–30.
17. McKenna KE. Central control of penile erection. Int J Impot Res. 1998;10 Suppl 1:S25–34.
18. Christ GJ, Lue T. Physiology and biochemistry of erections. Endocrine. 2004;23(2–3):93–100.
19. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am. 2005;32(4):379–95.
20. Saenz de Tejada I, Angulo J, Cellek S, et al. Physiology of erectile function. J Sex Med. 2004;1(3):254–65.
21. Fournier Jr GR, Juenemann KP, Lue TF, Tanagho EA. Mechanisms of venous occlusion during canine penile erection: an anatomic demonstration. J Urol. 1987;137(1):163–7.
22. Andersson KE. Neurophysiology/pharmacology of erection. Int J Impot Res. 2001;13 Suppl 3:S8–17.
23. Saenz de Tejada I, Kim N, Lagan I, Krane RJ, Goldstein I. Regulation of adrenergic activity in penile corpus cavernosum. J Urol. 1989;142(4):1117–21.
24. Lue TF. Erectile dysfunction. N Engl J Med. 2000;342(24):1802–13.
25. Berridge MJ. Inositol trisphosphate and calcium signalling. Nature. 1993;361(6410):315–25.
26. Cellek S, Rees RW, Kalsi J. A Rho-kinase inhibitor, soluble guanylate cyclase activator and nitric oxide-releasing PDE5 inhibitor: novel approaches to erectile dysfunction. Expert Opin Investig Drugs. 2002;11(11):1563–73.
27. The WMP, Lecture AA. The Ayerst award lecture 1990. Calcium-dependent mechanisms of regulation

of smooth muscle contraction. Biochem Cell Biol. 1991;69(12):771–800.
28. Rees RW, Ziessen T, Ralph DJ, Kell P, Moncada S, Cellek S. J., Kell P, Moncada S, Cellek S. Human and rabbit cavernosal smooth muscle cells express Rho-kinase. Int J Impot Res. 2002;14(1):1–7.
29. Somlyo AP, Somlyo AV. Signal transduction by G-proteins, rho-kinase and protein phosphatase to smooth muscle and non-muscle myosin II. J Physiol. 2000;522(Pt 2):177–85.
30. Wang H, Eto M, Steers WD, Somlyo AP, Somlyo AV. RhoA-mediated Ca2+ sensitization in erectile function. J Biol Chem. 2002;277(34):30614–21.
31. Ignarro LJ, Bush PA, Buga GM, Wood KS, Fukuto JM, Rajfer J. Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Commun. 1990;170(2):843–50.
32. Saenz de Tejada I, Goldstein I, Azadzoi K, Krane RJ, Cohen RA. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med. 1989;320(16):1025–30.
33. Bors E, Comarr AE. Neurological disturbances in sexual function with special reference to 529 patients with spinal cord injury. Urol Surv. 1960;10:191–222.
34. Comarr AE. Sexual concepts in traumatic cord and cauda equina lesions. J Urol. 1971;106(3):375–8.
35. Chapelle PA, Durand J, Lacert P. Penile erection following complete spinal cord injury in man. Br J Urol. 1980;52(3):216–9.
36. Luiten PG, ter Horst GJ, Karst H, Steffens AB. The course of paraventricular hypothalamic efferents to autonomic structures in medulla and spinal cord. Brain Res. 1985;329(1–2):374–8.
37. Sawchenko PE, Swanson LW. Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat. J Comp Neurol. 1982;205(3):260–72.
38. Wagner CK, Clemens LG. Projections of the paraventricular nucleus of the hypothalamus to the sexually dimorphic lumbosacral region of the spinal cord. Brain Res. 1991;539(2):254–62.
39. Argiolas A, Gessa GL. Central functions of oxytocin. Neurosci Biobehav Rev. 1991;15(2):217–31.
40. Argiolas A, Melis MR. Oxytocin-induced penile erection. Role of nitric oxide. Adv Exp Med Biol. 1995;395:247–54.
41. MacLean PD, Ploog DW. Cerebral representation of penile erection. J Neurophysiol. 1962;25:29–55.
42. Liu YC, Salamone JD, Sachs BD. Impaired sexual response after lesions of the paraventricular nucleus of the hypothalamus in male rats. Behav Neurosci. 1997;111(6):1361–7.
43. Yanagimoto M, Honda K, Goto Y, Negoro H. Afferents originating from the dorsal penile nerve excite oxytocin cells in the hypothalamic paraventricular nucleus of the rat. Brain Res. 1996;733(2):292–6.
44. Giuliano F, Rampin O. Central neural regulation of penile erection. Neurosci Biobehav Rev. 2000;24(5):517–33.
45. MacLean PD, Denniston RH, Dua S. Further studies on cerebral representation of penile erection: caudal thalamus, midbrain, and pons. J Neurophysiol. 1963;26:274–93.
46. Paredes RG, Baum MJ. Role of the medial preoptic area/anterior hypothalamus in the control of masculine sexual behavior. Annu Rev Sex Res. 1997;8:68–101.
47. Courtois FJ, Macdougall JC. Higher CNS control of penile responses in rats: the effect of hypothalamic stimulation. Physiol Behav. 1988;44(2):165–71.
48. Oomura Y, Yoshimatsu H, Aou S. Medial preoptic and hypothalamic neuronal activity during sexual behavior of the male monkey. Brain Res. 1983;266(2):340–3.
49. Liu YC, Salamone JD, Sachs BD. Lesions in medial preoptic area and bed nucleus of stria terminalis: differential effects on copulatory behavior and noncontact erection in male rats. J Neurosci. 1997;17(13):5245–53.
50. Stefanick ML, Davidson JM. Genital responses in noncopulators and rats with lesions in the medical preoptic area or midthoracic spinal cord. Physiol Behav. 1987;41(5):439–44.
51. McKenna KE. Some proposals regarding the organization of the central nervous system control of penile erection. Neurosci Biobehav Rev. 2000;24(5):535–40.
52. Chang AY, Kuo TB, Chan JY, Chan SH. Concurrent elicitation of electroencephalographic desynchronization and penile erection by cocaine in the rat. Synapse. 1996;24(3):233–9.
53. Chen KK, Chan JY, Chang LS, Chen MT, Chan SH. Elicitation of penile erection following activation of the hippocampal formation in the rat. Neurosci Lett. 1992;141(2):218–22.
54. Marson L, McKenna KE. The identification of a brainstem site controlling spinal sexual reflexes in male rats. Brain Res. 1990;515(1–2):303–8.
55. Tang Y, Rampin O, Giuliano F, Ugolini G. Spinal and brain circuits to motoneurons of the bulbospongiosus muscle: retrograde transneuronal tracing with rabies virus. J Comp Neurol. 1999;414(2):167–92.
56. Veronneau-Longueville F, Rampin O, Freund-Mercier MJ, et al. Oxytocinergic innervation of autonomic nuclei controlling penile erection in the rat. Neuroscience. 1999;93(4):1437–47.
57. Melis MR, Spano MS, Succu S, Argiolas A. The oxytocin antagonist d(CH2)5Tyr(Me)2-Orn8-vasotocin reduces non-contact penile erections in male rats. Neurosci Lett. 1999;265(3):171–4.
58. Bjorklund A, Lindvall O, Nobin A. Evidence of an incerto-hypothalamic dopamine neurone system in the rat. Brain Res. 1975;89(1):29–42.

59. Skagerberg G, Lindvall O. Organization of diencephalic dopamine neurones projecting to the spinal cord in the rat. Brain Res. 1985;342(2):340–51.
60. Pehek EA, Thompson JT, Eaton RC, Bazzett TJ, Hull EM. Apomorphine and haloperidol, but not domperidone, affect penile reflexes in rats. Pharmacol Biochem Behav. 1988;31(1):201–8.
61. Hull EM, Eaton RC, Markowski VP, Moses J, Lumley LA, Loucks JA. Opposite influence of medial preoptic D1 and D2 receptors on genital reflexes: implications for copulation. Life Sci. 1992;51(22):1705–13.
62. Warner RK, Thompson JT, Markowski VP, et al. Microinjection of the dopamine antagonist cis-flupenthixol into the MPOA impairs copulation, penile reflexes and sexual motivation in male rats. Brain Res. 1991;540(1–2):177–82.
63. Argiolas A, Collu M, D'Aquila P, Gessa GL, Melis MR, Serra G. Apomorphine stimulation of male copulatory behavior is prevented by the oxytocin antagonist d(CH2)5 Tyr(Me)-Orn8-vasotocin in rats. Pharmacol Biochem Behav. 1989;33(1):81–3.
64. Tang Y, Rampin O, Calas A, Facchinetti P, Giuliano F. Oxytocinergic and serotonergic innervation of identified lumbosacral nuclei controlling penile erection in the male rat. Neuroscience. 1998;82(1): 241–54.
65. Bitran D, Hull EM. Pharmacological analysis of male rat sexual behavior. Neurosci Biobehav Rev. 1987;11(4):365–89.
66. Bancila M, Verge D, Rampin O, et al. 5-Hydroxytryptamine2C receptors on spinal neurons controlling penile erection in the rat. Neuroscience. 1999;92(4):1523–37.
67. Chen KK, Chan SH, Chang LS, Chan JY. Participation of paraventricular nucleus of hypothalamus in central regulation of penile erection in the rat. J Urol. 1997;158(1):238–44.
68. Melis MR, Argiolas A. Role of central nitric oxide in the control of penile erection and yawning. Prog Neuropsychopharmacol Biol Psychiatry. 1997;21(6):899–922.
69. Sato Y, Christ GJ, Horita H, Adachi H, Suzuki N, Tsukamoto T. The effects of alterations in nitric oxide levels in the paraventricular nucleus on copulatory behavior and reflexive erections in male rats. J Urol. 1999;162(6):2182–5.
70. Sato Y, Horita H, Kurohata T, Adachi H, Tsukamoto T. Effect of the nitric oxide level in the medial preoptic area on male copulatory behavior in rats. Am J Physiol. 1998;274(1 Pt 2):R243–7.
71. Melis MR, Succu S, Iannucci U, Argiolas A. Oxytocin increases nitric oxide production in the paraventricular nucleus of the hypothalamus of male rats: correlation with penile erection and yawning. Regul Pept. 1997;69(2):105–11.
72. Melis MR, Succu S, Mauri A, Argiolas A. Nitric oxide production is increased in the paraventricular nucleus of the hypothalamus of male rats during non-contact penile erections and copulation. Eur J Neurosci. 1998;10(6):1968–74.
73. Argiolas A, Melis MR, Murgia S, Schioth HB. ACTH- and alpha-MSH-induced grooming, stretching, yawning and penile erection in male rats: site of action in the brain and role of melanocortin receptors. Brain Res Bull. 2000;51(5):425–31.
74. Wikberg JE. Melanocortin receptors: perspectives for novel drugs. Eur J Pharmacol. 1999;375(1–3):295–310.
75. Argiolas A, Melis MR. Central control of penile erection: role of the paraventricular nucleus of the hypothalamus. Prog Neurobiol. 2005;76(1):1–21.
76. Wessels H. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. Int J Impot Res. 2000;12(4):74–9.
77. Giuliano F, Rampin O, Brown K, Courtois F, Benoit G, Jardin A. Stimulation of the medial preoptic area of the hypothalamus in the rat elicits increases in intracavernous pressure. Neurosci Lett. 1996;209(1):1–4.
78. Melis MR, Stancampiano R, Argiolas A. Nitric oxide synthase inhibitors prevent N-methyl-D-aspartic acid-induced penile erection and yawning in male rats. Neurosci Lett. 1994;179(1–2):9–12.
79. Melis MR, Stancampiano R, Argiolas A. Penile erection and yawning induced by paraventricular NMDA injection in male rats are mediated by oxytocin. Pharmacol Biochem Behav. 1994;48(1):203–7.
80. de Groat WC, Booth AM. Neural control of penile erection. In: Maggi CA, editor. The autonomic nervous system. London: Harwood Academic Publishers; 1993. p. 465–524.
81. Bozkurt M, Gocmez C, Soylemez H, Daggulli M, Em S, Yildiz M, Atar M, Bozkurt Y, Ozbey I. Association between neuropathic pain, pregabalin treatment, and erectile dysfunction. J Sex Med. 2014;11(7):1816–22.
82. Melis MR, Succu S, Spano MS, Argiolas A. Morphine injected into the paraventricular nucleus of the hypothalamus prevents noncontact penile erections and impairs copulation: involvement of nitric oxide. Eur J Neurosci. 1999;11(6):1857–64.
83. Jain NK, Singh A, Kulkarni SK. Sildenafil-induced peripheral analgesia and activation of the nitric oxide–cyclic GMP pathway. Brain Res. 2001;909(1-2):170–8.
84. Yoon MH, Park KD, Lee HG, Kim WM, An TH, Kim YO, Huang LJ, Hua CJ. Additive antinociception between intrathecal sildenafil and morphine in the rat formalin test. J Korean Med Sci. 2008;23(6):1033–8.
85. Mixcoatl-Zecuatl T, Aguirre-Bañuelos P, Granados-Soto V. Sildenafil produces antinociception and increases morphine antinociception in the formalin test. Eur J Pharmacol. 2000;400(1):81–7.

Psychological Aspects of Erectile Dysfunction

3

Michael A. Perelman and Daniel N. Watter

Introduction

While penile erection is often thought of as being a primarily physical event, there are myriad psychological factors that contribute to both attaining and maintaining penile tumescence. A complete understanding of the processes of erectile function and dysfunction requires not only an understanding of the physical and psychological factors that contribute to erection but how these factors interact and combine to produce the male erectile response. This chapter will focus on the psychological factors that often interfere with the ability to achieve and/or maintain penile erection suitable for a satisfactory sexual experience for both the man and his partner. While the mental health clinician may wish to consult the latest edition of the Diagnostic and Statistical Manual of Mental Disorders [1] for diagnostic criteria, this chapter is primarily focused on increasing the medical practitioner's awareness of the psychosocial factors to be considered in order to provide a more successful and satisfying treatment experience for the man and his partner suffering with this sexual dysfunction.

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The Psychological Assessment

Assessment begins with the recognition that men often want a discussion to take place with their physician about their sexual issues. Yet, it is often extraordinarily difficult for a man suffering from ED to initiate it [2]. Not only might a man be embarrassed about admitting to such difficulty, he may fear a judgmental or dismissive reaction from his healthcare provider. In fact, these men may often feel quite "broken" and often report feeling as if they are not a "real man" [3]. Whether the cause of a man's erectile problems is physical or psychological, their ED will have a psychogenic component, even if the ED was initially the result of constitution, illness, surgery, or other therapy. Minimally almost all of these men will experience some degree of secondary psychological distress [4]. Many of these men have lost confidence in their ability to function sexually and have become sexually avoidant. Sexual avoidance often leads to avoidance of affection as well. This will likely have led to significant relationship problems as partners often worry that they have become unattractive to the man, the man has fallen out of love with them or is interested in another partner, etc. Clearly, the man

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sitting in front of his physician has a complicated story to tell. As a result, the physician must realize that taking the time to allow the man to completely tell his story is of the utmost importance. Yet, this can be quite challenging in this day and age of medical practice (at least in the United States) where office visits have become more rushed and time limited, and medical/sexual history taking may suffer.

The psychological assessment of erectile dysfunction encompasses both individual and relationship factors. Mental health professionals will look at the man's sexual history, as well as the presence of any comorbid psychiatric conditions. While the typical medical office visit may not allow for a thorough discussion of the multiple factors involved in a complete assessment, there are some specific questions the medical practitioner may find particularly useful to ask [5, 6]. As with any other chief complaint, the physician will want to inquire as to the duration and the circumstances of the man's erectile difficulties. For example, it would be important to know if the ED was lifelong or acquired (i.e., when did the patient first begin to notice his erectile difficulties). Also important is whether the ED is generalized or situational (i.e., does this occur in all situations, only with a particular partner, or only with intercourse but not other types of sexual activity, etc.). Perhaps one of the greatest indicators of a predominantly psychologically based case of ED is the timing of the erectile loss. It is not uncommon for the man experiencing ED to describe a pattern of good erectile functioning until, or shortly after, the point of penetration. These men report ease of penile tumescence followed by extended periods of foreplay. However, as penetration looms, the man's erection begins to fade. This is a hallmark presentation of psychological conflict and may be a function of any combination of the following: performance anxiety, concerns about the relationship, commitment, loss of autonomy, or numerous other psychological concerns. Additionally, some questions about the timing of the onset of the difficulty can also be of great diagnostic value. Many men report good erectile functioning until the occurrence of some "relationship-deepening event." These men often present with histories suggesting, "The sex was great until…". "Until" may mean moving in together, getting engaged, getting married, the birth of the first child, etc. All of these experiences could be considered a "relationship-deepening event." The following is an overview of the most important areas for consideration by the practicing physician.

Individual Factors

While it is difficult to isolate a singular causative agent in the assessment of ED, there are several areas of inquiry that may yield insight into the sexual psychology of the man the physician is evaluating. Sex researchers have determined that the following are frequently relevant psychological issues independently or in combination: performance anxiety (the level of anxiety experienced by the man regarding his ability, or lack thereof, to function sexually), past sexual trauma (i.e., sexual abuse), a history of negative sexual messages (i.e., as a result of familial or religious training that may induce guilt about sexual function/preferences), lack of adequate information of sexual skill, lack of adequate arousal to sexual stimuli, conflicts about gender identity/sexual orientation/or paraphilic interests, unrealistic expectations, other sexual dysfunctions (i.e., premature/delayed ejaculation), and/or other comorbid psychiatric disorders (i.e., depression, anxiety/panic disorder, bipolar illness, attention-deficit disorder, autism spectrum disorders, etc.) [7, 8].

While the abovementioned factors are often noted during a standard examination, equally often a psychologically based ED is *interpersonal rather* than *intrapersonal in its etiology.* For most of the men who are treated for ED, it is not the sex they have on their own that is problematic (i.e., masturbation). Rather it is the sex they have with a partner that, when problematic, may spur the desire for medical/psychological consultation. While the man may initiate this consult himself, it is very often his distressed partner who has urged him to do so [9]. Interpersonal factors that may result in

psychogenic ED include, but are not limited to, relationship conflict (i.e., anger), fear or avoidance of intimacy (i.e., fears of loss of autonomy and/or rejection), nonsexual relationship problems (i.e., problems with children and/or finances), and partner sexual dysfunction.

Impact of ED on the Man's Sexual Partner

One of the most overlooked factors in the assessment and treatment of ED is the impact that ED has on the man's sexual partner and their relationship [10]. Whether we are discussing heterosexual, homosexual, or bisexual relationships, healthcare professionals often neglect to include an adequate consideration of the man's partner in the assessment/treatment process.

ED within the context of a relationship affects all involved parties, not just the man experiencing the ED. Partners often wonder/worry about their potential contribution to the problem. Am I not attractive enough? Am I not a good-enough sex partner? Does may partner no longer love/desire me? Is he interested in someone else? Is he having an affair? Often, problems in the relationship occur because many men withdraw all affection from their partners when they are experiencing erectile difficulties. Many men in our offices have often commented that they hold back on affectionate gestures that might imply an interest in sexual activity for fear that they will be "unable to finish what I've started." As a result, a pattern of sexual avoidance becomes a pattern of affectionate avoidance as well. Regardless of the etiology of the ED, restoration of a satisfying sexual life for men in relationships will require repair of any relationship damage resulting from the disruption in their sexual/affectionate life.

Psychological Treatments

While there is no single psychological treatment for ED, many approaches have proven to be quite helpful. Often, the greatest determining factor for treatment choice is ascertained by an identification of the etiological factor(s) resulting in the erectile difficulties. For example, if the sexual problem is the result of depression, or another mood disorder, that condition will need to be targeted. Cognitive behavioral therapy (CBT), often combined with medication, is the treatment of choice for many. Similarly, if the ED is the result of anxiety (i.e., performance anxiety), relaxation exercises such as Masters and Johnson's *Sensate Focus* may be of particular use [11], as well as a variety of mindfulness exercises [12]. For the deeper-rooted problems of fear of abandonment, loss of autonomy, ambivalence about relationship commitment, in-depth psychodynamically oriented therapies may be most appropriate. When the primary issues appear to be a conflict between the couple, couple's therapy is often most indicated. Of course, as alluded to earlier, couple's therapy is likely to be indicated regardless of etiology since the ED has impacted the couple and their relationship, and repair of the relational damage will need to be addressed.

At the current time, there is a great deal of emphasis on therapies that combine both medical and psychological interventions. Many sex therapists today rely on a more "biopsychosocial" approach to treatment that recognizes the complex interaction of physiology, psychology, and relationship factors in the formation of both sexual health and dysfunction [12, 13]. Perelman [14] and Rosen [15] have both commented on the importance of combined therapies in which physicians and mental health professionals work collaboratively in an effort to provide comprehensive and efficient treatments. In fact, Perelman [16] has taken this a step further by advocating for a *transdisciplinary* perspective in the treatment of sexual difficulties in which the focus expands from combining the efforts of different practitioners, to one in which practitioners transcend the biases of their individual professions and integrate knowledge from other clinical and academic traditions.

While this chapter is focused on the psychological causes and treatments of ED, there is no reason to believe a single pathogenetic pathway to erectile dysfunction exists, and the benefits of the combination therapies mentioned are obvious. Besides the common sense appeal of such

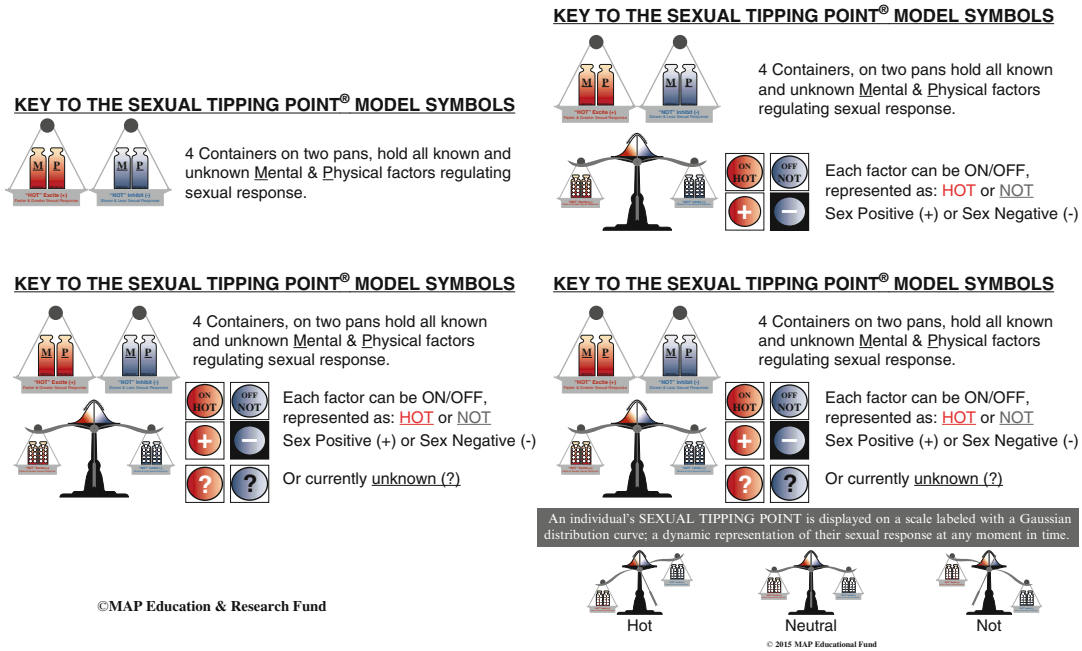

Fig. 3.1 How the STP explains sexual function and dysfunction: a sequential key to the STP model (Copyright © 2015 MAP Educational Fund. Used with permission)

models, there is as noted above an ever-expanding body of empirically based quantitative and qualitative evidence supporting a multidimensional conceptualization, especially in the areas of treatment optimization, treatment adherence, and continuation of recommended therapies [17–33].

The practicing physician may choose from a variety of biopsychosocial-behavioral and cultural models when contemplating erectile dysfunction, but sexual medicine and sex therapy have recently been most influenced by various "dual-control models" [34–39]. Bancroft and colleagues [34] remain the best known and researched of the various dual-control models. Yet, from our perspective when contemplating the clinical need for understanding etiology, diagnosis, and treatment, we find the Sexual Tipping Point® (STP) (Fig. 3.1) dual-control model particularly useful in its ability to illustrate both intra- and interindividual variability that characterizes erectile response and its impact on both men and their partners.[1] [30]

The Sexual Tipping Point® model easily illuminates the mind-body concept that mental factors can "turn you on" as well as "turn you off"; the same is true of the physical factors. The Sexual Tipping Point® is the characteristic threshold for an expression of a given sexual response. Therefore, an individual's Sexual Tipping Point® represents the cumulative impact of the interaction of a constitutionally established capacity to express a sexual response elicited by different types of stimulation as dynamically impacted by various psychosocial-behavioral and cultural factors. An individual's threshold will vary somewhat from one sexual experience to another, based on the proportional effect of all the different factors that determine that tipping point at a particular moment in time. For instance, the cartoon in Fig. 3.2 illustrates an individual suffering from a diminished erectile response [30].

Besides illustrating all etiological permutations, including normal *sexual balance*, the Sexual Tipping Point® concept is particularly useful for modeling treatment and can easily be used to explain risks and benefits for patients with erectile disorders. The STP model can be

[1] The Sexual Tipping Point model is the registered trademark of the MAP Education & Research Fund, a (501)(C3) public charity.

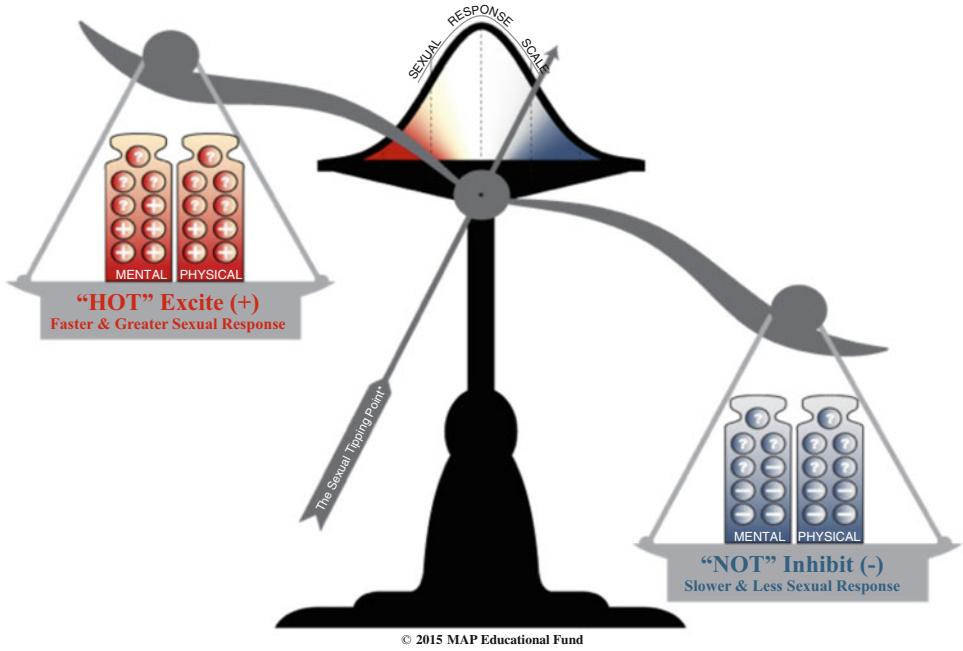

Fig. 3.2 STP illustrates diminished erectile response (Copyright ©2015 MAP Educational Fund. Used with permission)

used to teach patients where different treatment targets should be focused,depending on diagnosis of their etiological determinants. Typically expressed erroneous binary beliefs can be politely disabused, and the patient can be reassured that "no it is not all in your head" nor "all a physical problem." Reciprocally, their partner can be assured it is "not all their fault!" Teaching the STP model to the patient and partner can reduce patient and partner despair and anger, while providing hope through a simple explanation of how the problem's causes can be diagnosed, parsed, and "fixed." In fact, the Sexual Tipping Point® also allows for modeling of a variety of future treatments, including medical or surgical interventions not yet discovered or proven such as novel pharmacotherapy, genetic engineering, or nanotechnology [38]. This is illustrated in Fig. 3.3.

For those interested, mapedfund.org provides a video explanation of the STP model as well as continuously updated images and other resources which are all available for free download by healthcare professionals.

Talking to Patients About Sexual Issues

While there is no one way to best address these issues in medical practice, it is clear that patients will be receptive to talking to their physicians about their sexual problems [40] particularly if the physician initiates the conversation [2]. Indeed, most mental health professionals will report that the majority of their sex therapy referrals come directly from physicians. Consistent with current pharmaceutical advertising, many men consider their physician to be the primary source of assistance when confronting sexual problems such as erectile dysfunction [41]. This is especially so in the age of PDE-5 inhibitors since many men are hopeful that a simple prescription will alleviate their sexual distress. Yet

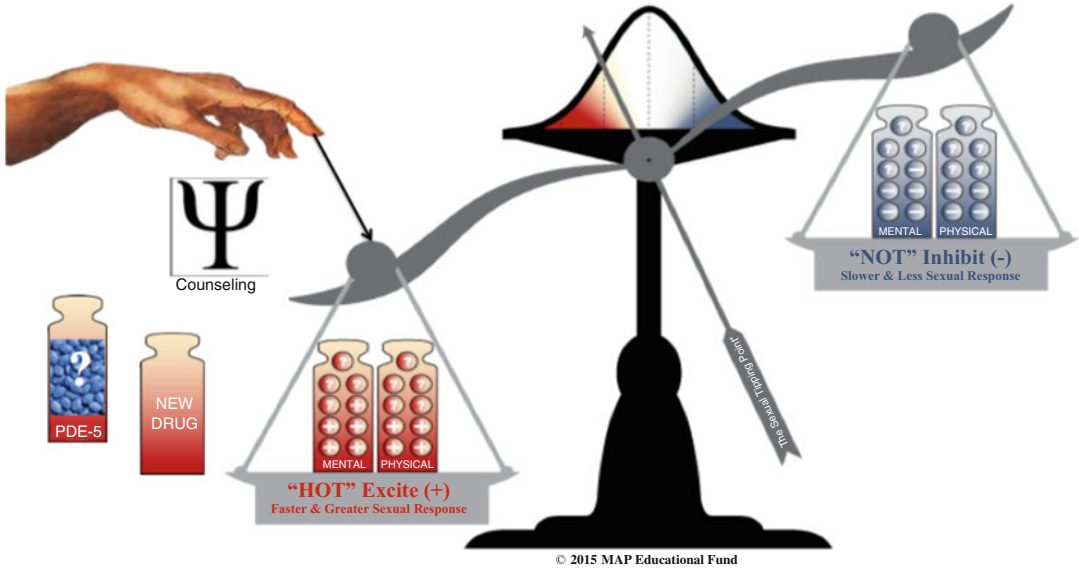

Fig. 3.3 Illustrating the elegant solution: STP depicts integrated treatment with a future medical therapy that is unknown today. For the metabolic syndrome patient. The ideal solution to balance risk/benefit (Copyright © 2015 MAP Educational Fund. Used with permission)

many physicians are still uncomfortable discussing sexual matters with their patients and often do not spend the necessary time to either inquire or address sexual concerns. This is quite unfortunate inasmuch as sex therapist Candace Risen [42] reminds us, "They [patients] dread being asked, but they long to be asked." Despite having had little training in medical school in the particulars of how to discuss sex with patients, physicians can still play a vital role in assisting ED patients to get the help they so desperately want. It is important to note that there are many possible levels of intervention for the practicing physician that do not require a large investment of time or specialized training in sexual medicine.

A physician might find another popular and user-friendly model helpful that was developed by psychologist, Jack Annon [43]. Annon termed his model the PLISSIT model in which he described several levels of intervention at which physicians can choose to respond to patients' sexual concerns. In this model, the letter "P" stands for *permission*, *which* involves the physician giving the patient permission to speak and voice their concerns about sex. This level is especially important, as patients often are unsure of whether or not their physician will be receptive to their concerns and may find discussing sexual difficulties such as ED embarrassing. Simply opening the door for the patient to feel welcome asking for advice and assistance can be highly therapeutic. The second level of intervention in the PLISSIT model is "LI" or *limited information.* Limited information may be some brief education about the physiology of erectile response, the "normalizing" of occasional erectile difficulties for most men, or some brief information about treatment options. "SS" stands for *specific instructions* in which the physician may make a specific suggestion for treatment such as oral medications, penile injections, penile prostheses, etc. These first three levels of intervention can be easily communicated to patients using the STP framework. Finally, the "IT" refers to *intensive therapy* in which the physician may believe that either the medical options alone have not been successful or the patient requires treatment for a detected comorbid mental health issue and makes a referral to a sex therapist or other mental health specialist.

Oftentimes, physicians report discomfort bringing up sexual issues with their patients. This

may be, in large part, because discussing sexual issues has historically been absent from the training of healthcare professionals [2]. However, as mentioned previously patients often want to discuss their sexual difficulties with their physicians; indeed that is the reason that many will seek out medical attention in the first place. According to Carroll [8], assuming the patient does not bring up sexual difficulties themselves, the physician can begin with an open-ended inquiry as to whether the patient has any sexual concerns. Something as simple as "How is your sexual life going?" or "Do you have any sexual concerns?" will go a long way in helping the patient to feel comfortable in bringing up their concerns. This type of question gives the patient permission to discuss such sensitive topics (recall the "P" from the PLISSIT model) and frames the issue in a nonjudgmental manner. Presenting with a nonjudgmental attitude is essential in assisting the patient to feel comfortable in opening up to his physician. Again, it is important to remember that patients want to discuss these matters with their physicians. When the physician is sensitive enough to this reality, the rest of the helping process will likely flow smoothly.

Psychological Issues in the Post-Viagra Era

There is little doubt that the advent of oral medications for the treatment of ED has created a tremendous paradigm shift in the way we think about the evaluation and treatment of this disorder. According to Rosen et al. [7], since the introduction of PDE-5 inhibitors in 1998, well over 100 million men worldwide have sought treatment for ED, and these drugs have become a first-line treatment. This has occurred for several reasons and has had both advantages and problems.

Sildenafil, tadalafil, and vardenafil (Viagra, Cialis, and Levitra) have become the ED treatment of choice for both physicians and patients for a variety of reasons. On the positive side, they have offered the hope and promise of effective treatment for ED that has encouraged more patients to seek treatment than ever before. Earlier medical treatments such as the vacuum constriction device, penile injections, and penile prostheses all had significant drawbacks in the eyes of many patients and their partners. The sheer simplicity of being able to quickly and easily "swallow a pill" has obvious appeal. And for many patients, these medications have been highly effective and easy to tolerate. The possibility of an effective treatment that is easy to use and is relatively safe has allowed many men and their partners to resume having sexual intercourse for the first time in many years. This has also made office practice easier for many physicians as it has allowed them to offer treatment quickly and easily without the need for an extensive and expensive evaluation process.

However, despite these seeming advantages, the use of oral medications has not been without its problems and critics. Marino [44] reminds us that all progress paves over some bit of knowledge or washes away some valuable aspect of practice. That is, with any new technological advance, a field inevitably loses some of the art attached to its craft [45]. Indeed, many physicians have lamented the fact that "quick and easy solutions" can easily overlook important medical and psychological factors that otherwise would have been attended to. For example, while time consuming and expensive, the work-ups patients used to receive would, on occasion, turn up evidence of cardiovascular and other diseases that now go undetected until they become highly problematic. In addition, the ease of obtaining oral medications for ED has led some physicians, and many patients, to erroneously assume that the treatment of ED will be simple, yet this is often not the case. Despite the ease of availability, the dropout rate for oral medication therapies for ED is still very high. This may be due to the price (these medications can be quite expensive and often not covered by health insurance, at least in the United States). While side effects and expense play a part, psychosocial, behavioral, and cultural obstacles can frequently be significant barriers to successful treatment. Unfortunately, this is exacerbated by the fact that many physicians are spending less time discuss-

ing sexual concerns with their patients and may dismiss them subsequent to a hastily obtained sex history and quickly written prescription. This may have the effect of making the man feel his physician has neither the time nor the interest to fully address his sexual concerns. While he may accept the suggestion of medication, if it does not adequately resolve his ED, the man will be much less likely to return for follow-up care than he would be if he left the office visit with the feeling that he was being heard and well attended to. As a result, the underlying psychological issues are left unresolved (i.e., relationship problems as an example), and at times even when the man's erections improve with medication, his sexual relationship may not [33].

The availability of oral medications as a treatment for ED has also led some sexuality professionals to express significant apprehension that sexuality and sexual function that will come be increasingly seen as a purely mechanical process that is easily amenable to a simple, "quick-fix" type of resolution [45–48]. This concern, which is also sometimes referred to as the *medicalization* of sexuality, may lead many physicians and their patients to ignore the complexity of the sexual/relational experience that is so central to the human condition. For many years, sex therapists have attempted to shift patients (especially their male patients) away from a limited one-dimensional view of sex as an exclusively goal-directed genital experience. All healthcare professionals and patients are best served when avoiding such an overly reductionist viewpoint.

It has been argued [45] that the recent excitement about the possibility of successful restoration of erectile dysfunction via the use oral medications has led to some unfortunately unrealistic expectations on the part of many male patients. It is well known among physicians that the aging process will lead to inevitable changes in male sexual response and function. Specifically, erectile difficulties and inconsistencies will become increasingly common as a man ages. While some patients may have experienced disappointment, when informed of this normal effect of aging, they had been generally accepting of this reality. However, in the post-Viagra age, many men now have the promise of not only restored erectile function but the illusion of a restored youth, as well. While some may not initially see the potential harm in a treatment that may allow a man to feel more youthful, physicians and other healthcare professionals must consider the possibility that we are offering an unrealistic (and perhaps unfair) picture to patients that reinforces the notion that youth is "good" and aging is "bad." Rather than supporting our patients in the acceptance of natural and healthy aging, we may inadvertently be doing them a disservice as they struggle to come to terms with normal bodily changes [49].

A similar concern relates to our treatment of men with prostate cancer. Many men enter surgical treatment for prostate cancer with the high (perhaps unrealistic) expectation that their erectile function will be completely restored. In this day and age of surgical advances and "nerve-sparing" prostatectomy, many men assume that following radical prostatectomy, they will be able to resume their sexual lives as before. Unfortunately, too few physicians do enough to correct this mistaken assumption. Even with advanced surgical technique, penile rehabilitation protocols, and oral medications to treat ED, fewer men then one would hope regain complete erectile function, and controversy over the most efficacious postsurgical protocols continues to this day [49]. Most prostate cancer surgical patients will experience a long healing process (perhaps years), weaker, or less rigid erections, and the loss of "erections on demand." Many men feel unprepared for these changes, sometimes because they chose to be overly optimistic regarding surgical outcome. However, it is also likely that many men feel unprepared because their physicians were unwilling, or unable, to have the conversation with these men that assist them in having a more realistic assessment of their post-surgical sexual lives. As mentioned earlier, many physicians often feel uncomfortable discussing sexual matters with patients, and some may fear that having such a conversation may deter men from having a surgical treatment that might be medically in the patients' best interests. Whatever the reason, many men enter mental health treatment feeling angry, depressed, frustrated, and "broken." Sometimes, these men feel that they

are no longer a "real man" [51]. Physicians taking more time to have these important conversations with these men and their partners prior to surgery would do so much good in minimizing the distress over this surgical sequela.

One of the strongest voices for a more realistic mental health model for men (especially aging men or physically compromised men) is Barry McCarthy, Ph.D., and his frequent collaborator, Michael Metz, Ph.D. McCarthy and Metz [52] were strong advocates for what they refer to as the *Good-Enough Sex model.* According to McCarthy and Metz, the focus of sexual activity should be less about performance and more about pleasure. Their Good-Enough Sex model has 12 essential principles:

1. Sex is a good element in life, an invaluable part of the man's and couple's comfort, intimacy, pleasure, and confidence.
2. Relationship and sexual satisfaction are the ultimate developmental focus. The couple is an intimate team.
3. Realistic age-appropriate sexual expectations are essential for couple sexual satisfaction.
4. Good physical health and healthy behavioral habits are vital for sexual health. The man values his own and his partner's sexual body.
5. Relaxation is the foundation for pleasure and function.
6. Pleasure is as important as function.
7. Valuing variable, flexible sexual experiences and abandoning the "need" for perfect performance inoculate the man and couple against sexual dysfunction by overcoming performance pressure, fears of failure, and rejection.
8. The five purposes for sex are integrated into the couple's sexual relationship (shared pleasure and enjoyment, a means to deepen and reinforce intimacy and satisfaction, a tension reducer to deal with the stresses of a shared life, a means to reinforce self-esteem and confidence, and the traditional biological function of procreation).
9. The couple integrates and flexibly uses the three sexual arousal styles (partner interaction, self-entrancement, and role enactment).
10. Gender differences and similarities are respectfully valued and mutually accepted.
11. Sex is integrated into the couple's real life and real life is integrated into their sexual relationship. Sexuality is developing, growing, and evolving throughout life.
12. Sexuality is personalized. Sex can be playful, spiritual, and special.

While each of these points has great potential utility in improving the sex life of the man and his partner, numbers 3, 6, and 7 have particular relevance for the aging man and the prostate cancer surgical patients.

Some Thoughts on Sexual and Cultural Diversity

Hall and Graham [53] suggest that much of what we know about sexual problems and sexual medicine comes from Western societies (the United States, Canada, Britain, and Western Europe), where sex research was first established. As a result, there is a dearth of research on sexual problems in non-Western cultures. They further remind us that the ED treatment dropout rate for ethnic minorities is extraordinarily high. It is important for the practicing physician to be mindful of the fact what is regarded as "problematic" sexual functioning may be normative in a different cultural context. It is extremely difficult to be aware of all of our cultural biases and assumptions. This, again, highlights the need for physicians to take the time to actively listen to what their patient's complaints are, as well as clearly ascertain the solution they are seeking. The sexual goal of a Western physician may not be the same as the sexual goal of a non-Western patient and his partner. Oftentimes, treatment suggestions we make may be seen as culturally or religiously unacceptable to the man we are treating. Ensuring that we have the "buy-in" and cooperation of our patients is essential to good treatment outcome, especially with regard to sexual problems such as ED.

Sensitivity to psychological needs of sexual minorities is also necessary for physicians treating ED. Nichols [54] asserts that since the early days of the AIDS epidemic, research on the sexuality of gay males has focused almost exclusively on HIV transmission and prevention. Male sexual dysfunction has received relatively little attention. Sandfort and de Keizer [55] actually found that reports of ED were higher for gay men than straight men, and Hart, Wolitski, and Purcell [56] also found high ED rates in gay men. Moser [57] reports that while medicine has recently begun to address the sexual concerns of gay and bisexual men, other sexual minorities (transgender, kink) have received little or no attention. According to Moser, many men suffering with ED are fearful of being judged negatively by their physicians due to their sexual lifestyles and thus are often likely to postpone seeking treatment for their ED, or may forego treatment altogether. Clearly, this is an unfortunate situation and one that future training of physicians needs to address. For the practicing physician, suffice to say that it is highly likely that you will come across members of cultural and sexual minorities who are suffering with ED and desirous of treatment. It is imperative that the practicing physician makes no assumptions about the sexuality of the man he or she is seeing for consultation. In order to adequately address the medical and psychological sexual needs of such patients, a nonjudgmental attitude, a welcoming office environment, and a willingness to take the time to truly listen to the patient's story are essential. Below some case histories illustrate many of the principles described within this chapter.

Case Examples

Case #1: Bob: A Case of Misunderstanding

Bob was a 25-year-old heterosexual male who was referred for sex therapy by his urologist. Bob reported being unable to complete sexual intercourse because he was unable to sustain penile erection until the point of orgasm/ejaculation. Bob's physician briefly listened to his complaints, did a cursory physical examination, and prescribed a trial of a PDE-5 inhibitor. Bob had seen another urologist about a year before and received the same treatment recommendation. After approximately 2 months, Bob returned to his urologist saying that the medication did not resolve his problem. As a result, Bob received a referral for sex therapy and called to arrange a consultation.

At Bob's initial sex therapy visit, he gave a detailed description of his symptoms. It soon became clear that Bob's dysfunction was not ED, but rather delayed ejaculation. What Bob was unable to successfully convey to his urologist was the fact that while he was unable to maintain his erection until the completion of sexual intercourse, he would routinely engage in intercourse for up to 60 min! He would eventually be unable to continue and would stop intercourse before orgasm/ejaculation would occur. The recommendation of the PDE-5 inhibitor obviously was not going to effectively address Bob's difficulties. Sex therapy then proceeded to treat the DE condition, and Bob was eventually able to have sexual intercourse in a much more satisfying manner.

Comment: This case highlights two very important factors in the assessment and treatment of male sexual dysfunction. The most obvious is the importance of carefully listening to the patient's complaint and taking the time to obtain a detailed history and description of the problem. If Bob's physician had done this, it would have likely led Bob to an effective course of treatment much sooner. Bob was fortunate that he did not give up his search for assistance. Many patients would have become frustrated with the process and lack of success and as a result, would continue to suffer needlessly. The second notable feature of this case is how difficult it is for many patients to accurately articulate their symptoms. Many patients lack the vocabulary to effectively convey the details of their situation. Bob had never heard of DE, and truly believed he suffered from ED. His lack of clinical sophistication highlights even more so the need for physicians to take careful, comprehensive sex histories and to educate patients.

Case #2: Jim: An Example of Combination Treatment

Jim was a 44-year-old, heterosexual, married man who was referred for sex therapy by his urologist. Jim had been experiencing intermittent erectile dysfunction for approximately 2 years, but the frequency of erectile difficulties was increasing. Jim's urologist did a history and examination and was unable to identify a medical explanation for his ED. However, he wisely recommended a course of sex therapy to see if that would improve Jim's sexual difficulties.

Jim reported being happily married for 15 years. In describing his symptoms, he reported easily achieving penile erection, but would lose penile rigidity while attempting to begin sexual intercourse. This situation was distressing to both Jim and his wife, as she feared he no longer found her physically attractive and/or was no longer in love with her. Jim assured us both that this was far from the case.

By way of history, Jim's parents had a difficult marriage. Jim's mother left the family when he was 5 years old complaining that Jim's father was a business failure and she wanted better for herself. In retrospect, Jim believes his mother was frustrated in her own life as she became pregnant, married very young, and had no opportunity to pursue the career of her dreams. Still, as a young boy, Jim deeply felt the pain of abandonment.

Jim reports his erectile difficulties began during a down period in his business. Both he and his wife were concerned about this, but Jim found himself especially agitated. He had assumed that his erectile difficulties were the result of the stress of business complications, but even as business improved his erectile functioning remained problematic. During psychotherapy, Jim was able to see how his business setbacks and wife's concerns triggered in him fears of abandonment, and he reported oftentimes feeling panicked that his wife would leave him. Of course, she had never expressed any such sentiments, but Jim recalled feeling that his mother's abandonment seemed to come without notice and was fearful that his wife would one day simply not be home when he arrived. In psychotherapy we were able to work through the unresolved pain of Jim's abandonment as a child, and much of his anxiety subsided. However, his sexual difficulties improved only slightly. Jim now had lost confidence in his ability to function sexually and found himself experiencing high degrees of performance anxiety. In addition, since Jim's erectile problems persisted, his wife felt more convinced than ever that he had lost her attraction to her. We began to engage in several sessions of couple's therapy in an effort to repair the damage that had been done to the relationship and to alleviate some of Jim's performance fears. In addition, we worked with Jim's urologist who prescribed a PDE-5 inhibitor and Jim found that to be helpful with erections. As Jim's confidence returned, we gradually reduced the dosage of the PDE-5 inhibitor until Jim was able to function well without any medication. Individual and couple's therapy continued for several more months until both Jim and his wife felt comfortable that the situation had been successfully resolved.

Comment: This case is a good illustration of the importance of both combined therapy and couple's therapy in the successful resolution of many cases of ED. In addition to working through Jim's conflicts in individual therapy, this case demonstrates the benefits of the cooperative interaction between the urologist and the sex therapist. As mentioned earlier in this chapter, combined treatments often have the greatest efficacy in addressing the needs of the man struggling with ED. In addition, this case clearly illustrates the importance of considering the partner in the treatment process. Jim and his wife were struggling to understand and repair the damage done to their relationship. Jim's wife needed to discuss and resolve her fears and concerns that she was no longer attractive to him. Beyond her concerns, the fractures that had occurred in their relationship due to the fighting and resultant distancing between them had to be therapeutically corrected. It is unlikely that this case would have had a successful outcome without attention to these additional factors. It was to the physician's credit that subsequent to careful

diagnosis, an appropriate referral sex therapy was both given which resulted in a successful treatment.

Case #3: Andrew: A Case of Kinky Desire

Andrew was a 37-year-old single male who had never successfully completed sexual intercourse. He reported that his early attempts at sexual intercourse resulted in erectile loss, and as a result he had avoided sexual opportunities for the past several years. Recently, he had met a new woman with whom he believed he wanted to have an intimate relationship. He had been able to avoid sex for several months, but she eventually sensed something was amiss. He had told her he had ED and she was kind and sympathetic. She encouraged him to engage sexually with her, but he experienced the same sexual frustration with erectile insufficiency. He would achieve only a partial erection, and that erection would fade even further as sex progressed. His new girlfriend encouraged him to seek medical help, hoping that a PDE-5 inhibitor would be helpful to Andrew.

Andrew met with a urologist who did a history and examination. He found no evidence of organic dysfunction and suggested Andrew try a PDE-5 inhibitor. Andrew took some samples and a prescription, but he never used them saying he was not a "medication" type of person. As frustration mounted for both Andrew and his girlfriend, Andrew became increasingly distressed at the possibility she would leave him. Fortunately his urologist was able to elicit this information from him during the 1-month follow-up session that had been previously scheduled for Andrew, which allowed the urologist to make an opportune referral for sex therapy.

Andrew presented for therapy as a highly anxious and agitated man. His distress was palpable. Careful questioning about his sexual history encouraged Andrew to finally reveal to his therapist the details that he did not reveal to his urologist, namely, that his sexual interests did not include the more "vanilla" types of sex. Andrew was aroused by fantasies of bondage and discipline. His sexuality was stirred by what is often referred to as BDSM (bondage and discipline, dominance and submission, sadomasochism). Unfortunately, Andrew was very conflicted about his sexual interests believing that others would see them as unacceptable; indeed he often felt they were unacceptable to him as well. Andrew was concerned that he was somehow a sexual "freak" and could never reveal his secret desires to anyone. Interestingly, when masturbating to BDSM fantasies, Andrew experienced good, solid erections and satisfying orgasms.

Much of Andrew's psychotherapy focused on helping him to better accept himself and his sexual interests. In addition, Andrew was helped to take some risks in revealing himself to his new girlfriend. Obviously, Andrew was quite tentative and initially resistant to moving in this direction, but as the relationship progressed, he began to gently introduce the topic of kinky sex into their discussions. Much to his surprise, his girlfriend was quite receptive to sexual experimentation, and they began to explore the type of sex Andrew found most erotic and arousing. This led to his first successful sexual intercourse, and the couple was able to integrate some BDSM into their lovemaking. Interestingly, this also allowed Andrew to learn to enjoy non-kinky sex as well, although his primary sexual interests remain of the kink variety.

Comment: This case illustrates the difficulty many patients experience in fully revealing their sexual interests to their physicians and the importance for the physician to identify when to refer. Andrew felt great shame and embarrassment regarding his interest in kinky sex and feared he would be judged negatively for his proclivities. As a result, he was unwilling to reveal himself to his urologist, who was naturally unable to effectively intervene as he was without adequate information. As mentioned previously, many patients with nonstandard sexual interests delay, or avoid, seeking medical assistance for their ED. Regrettably, there may have been little Andrew's urologist could have done differently, yet Andrew's case illuminates the importance of physicians being nonjudgmental and accepting of their patients' sexuality. It also highlights the

value for physicians to provide follow-up care to patients following office visits in an effort to verify if medical suggestions were taken, and if not, why they may have been resisted. Finally, when a patient is unwilling to disclose important information regarding their sexuality, often a referral to a sex therapist may unlock that seeming conundrum.

Case #4: Stanley: A Case of ED Following Radical Prostatectomy

Stanley was a 66-year-old married heterosexual male who had undergone a radical prostatectomy 3 years prior to sex therapy consultation. Stanley reported being happily married to his wife of 38 years, and they had a mutually satisfying sex life prior to his treatment for prostate cancer. Despite a nerve-sparing procedure having been performed at a major medical center, 3-year postsurgery, Stanley's erectile functioning was still problematic and he was becoming increasingly frustrated and angry. He had been taking a PDE-5 inhibitor daily for over a year, with no improvement. In consultation with his urologist, both agreed that a referral for sex therapy might be overdue.

Stanley and his wife presented for sex therapy as a couple in distress. While Stanley was upset about his continued erectile difficulties, his wife was more concerned about his level of anger and distancing from her. Stanley's wife was focused on her relief that he was a cancer survivor, and said that she didn't care if they were able to resume having a sexual relationship. She was thankful to still have Stanley alive and couldn't understand why he was not similarly grateful. Stanley, on the other hand, felt betrayed by his urologist. Despite evidence to the contrary suggested to him presurgically, Stanley believed that his postsurgical erectile functioning adjustment would be better than it was, and he now doubted his decision to having gone forward with surgery. Stanley reported feeling "broken" and like "half of a man." Much of Stanley's psychotherapy focused on dealing with his anger and coming to terms with the fact that his sexuality would likely be quite different than he had expected.

Both Stanley and his wife did well with couple's therapy. Stanley's anger eventually receded, and his wife was a willing participant in exploring a new version of what their sexual life would be. Both eventually embraced McCarthy and Metz' idea of a Good-Enough Sex model of sexual functioning [52], and they began to reexperience the intimacy they had lost. After several months of psychotherapy, Stanley and his wife reported rediscovering the happiness they had feared was forever lost.

Comment: This case highlights several important concepts for the practicing physician. The psychological challenges that accompany ED following treatment for prostate cancer cannot be underestimated. So many men experience postsurgical disillusionment and feel misled about the prospects for postsurgical erectile functioning. Even those men who are able to regain erectile function that is suitable for sexual intercourse experience some distress over the fact that their erections, while perhaps sufficient for penetration, are not of the same quality as they were in presurgery. This case exemplifies the difficulty and challenges surgeons experience when a patient facing a life-threatening disease does not fully absorb the educational messages imbedded in the standard informed consent that is typically provided presurgically. It is a sobering reminder of the importance for explicit discussion that sets appropriate sexual expectations for prostate cancer patients and their partners prior to their treatment making decision. In addition, increased sensitivity to the psychological sequelae that often accompany even "successful" surgical outcomes is warranted.

Conclusions

Clearly, men experiencing ED will often present with myriad psychological concerns and issues. When these issues are properly explored by the practicing physician, greater treatment success and satisfaction will result for the patient, his partner, and the physician. The biopsychosocial-behavioral and cultural models of sexual dysfunction provide a compelling argument for

sexual medicine treatments that integrate sex counseling and medical and/or surgical treatments [13, 14]. The goal is not just to alleviate our patient's ED, but when possible to improve intimacy and relationships. This chapter has attempted to highlight the need for physicians to be on the alert for psychological causation, psychological complication, and an increased sensitivity to the importance of including the partner in treatment (when possible) in order to make treatment outcomes more positive for these patients. We hope this chapter has helped to make clear that whether ED is caused by psychological factors or not, most every man experiencing ED will have psychological issues that require attention. The healthcare professional who provides an integrated treatment will offer the most optimized approach and the most elegant solution [16]. We hope such a transdisciplinary perspective becomes the prevalent teaching model for all healthcare practitioners early in their training. Optimally, all healthcare practitioners will utilize a patient-centered holistic view of healing that integrates a variety of treatment approaches as needed for ED or other sexual dysfunction.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association Press; 2013.
2. Marwick C. Survey says patients expect little physician help on sex. JAMA. 1999;281(23):2173–4.
3. Watter DN. Psychological commentary for chapter 12: urologic/clinical evaluation and treatment of disorders of ejaculation. In: Libshultz LI, Giraldi A, Goldstein A, Perelman MA, editors. Sexual health in the couple: an integrated approach to sexual dysfunction in men and women. New York, NY: Springer; 2016.
4. Perelman MA. Rehabilitative sex therapy for organic impotence. In: Segraves T, Haeberle E, editors. Emerging dimensions of sexology. New York, NY: Praeger Publishers; 1984.
5. Althof SE, Rubio-Auriole E, Perelman MA. Standard operating procedures for taking a sexual history. J Sex Med. 2012;10(1):26–35.
6. Maurice WL. Sexual medicine in primary care. St. Louis, MO: Mosby; 1999.
7. Rosen RC, Miner MM, Wincze JP. Erectile dysfunction: integration of medical and psychological approaches. In: Binik YM, Hall KSK, editors. Principles and practice of sex therapy. 5th ed. New York, NY: Guilford Press; 2014.
8. Carroll RA. Psychological aspects of erectile dysfunction: a clinical guide. In: McVary KT, editor. Contemporary treatment of erectile dysfunction. New York, NY: Humana; 2011.
9. Shabsigh R, Laumann EO, Lockhart DC, Perelman MA. Drivers and barriers to seeking treatment for erectile dysfunction: a comparison of six countries. Br J Urol Int. 2004;94(7):1055–65.
10. Perelman MA. The impact of relationship variables on the etiology, diagnosis and treatment of erectile dysfunction. Adv Prim Care Med. 2007;3:3–6.
11. Masters WH, Johnson VE. Human sexual inadequacy. New York, NY: Little, Brown and Co; 1970.
12. Althof SE. What's new in sex therapy? J Sex Med. 2010;7:5–13.
13. Perelman MA. Integrated sex therapy: a psychosocial-cultural perspective integrating behavioral, cognitive, and medical approaches. In: Carson C, Kirby R, Goldstein I, Wylie K, editors. Textbook of erectile dysfunction. 2nd ed. London: Informa Healthcare; 2008.
14. Perelman MA. Psychosocial evaluation and combination treatment of men with erectile dysfunction. Urol Clin N Am. 2005;32(4):431–5.
15. Rosen RC. Erectile dysfunction: integration of medical and psychological approaches. In: Leiblum SR, editor. Principles and practice of sex therapy. 4th ed. New York, NY: Guilford Press; 2007.
16. Perelman MA. Advocating for a transdisciplinary perspective in sexual medicine. Curr Sex Health Rep. 2015;7(1):1–2.
17. Abdo C, Afif-Abdo J, Otani F, Machado A. Sexual satisfaction among patients with erectile dysfunction treated with counseling, sildenafil, or both. J Sex Med. 2008;5(7):1720–6.
18. Althof SE, Needle RB. Psychological factors associated with male sexual dysfunction: screening and treatment for the urologist [Review]. Urol Clin N Am. 2011;38(2):141–6.
19. Aubin S, Heiman J, Berger R, Murallo A, Yung-Wen L. Comparing sildenafil alone vs. sildenafil plus brief couples sex therapy on erectile dysfunction and couples' sexual and marital quality of life: a pilot study. J Sex Marital Ther. 2009;35(2):122–43.
20. Bach A, Barlow D, Wincze J. The enhancing effects of manualized treatment for erectile dysfunction among men using sildenafil: a preliminary investigation. Behav Ther. 2004;35:55–73.
21. Banner L, Anderson R. Integrated sildenafil and cognitive-behavior sex therapy for psychogenic erectile dysfunction: a pilot study. J Sex Med. 2007;4(4):1117–25.
22. Brock G, Carrier S, Casey R, Tarride J, Elliott S, Dugre H, Defoy I. Can an educational program

optimize PDE5i therapy? A case study of Canadian primary care practices. J Sex Med. 2007;4(5):1404–13.
23. Brotto L, Basson R, Luria M. A mindfulness-based group psychoeducational intervention targeting sexual arousal disorder in women. J Sex Med. 2008;5(1646-59):1646.
24. Brotto L, Heiman J, Goff B, Greer B, Lentz G, Swisher E, Van Blaricom A. A psychoeducational intervention for sexual dysfunction in women with gynecologic cancer. Arch Sex Behav. 2008;37(2):317–29.
25. Brotto L, Woo J. Cognitive-behavioral and mindfulness-based therapy for low sexual desire. In: Leiblum S, editor. Treating sexual desire disorders: a clinical casebook. New York, NY: Guilford Press; 2010.
26. Goldstein A, Pukall C, Goldstein I, editors. Female sexual pain disorders: evaluation and management. Oxford: Blackwell Publishing; 2009.
27. Mahmoud A, Drake RJ, Lewis SW, Hayhurst KP, Barnes TRE. The ANNSERS (antipsychotic non-neurological side effects rating scale): validation of sexual side-effect measurement. Ther Adv Psychopharmacol. 2011;1(4):97–100.
28. McCabe M, Price E, Piterman L, Lording D. Evaluation of an internet-based psychological intervention for the treatment of erectile dysfunction. Int J Impot Res. 2008. doi:10.1038/ijir.2008.3.
29. Perelman MA. The sexual tipping point: a model to conceptualize etiology and combination treatment of female and male sexual dysfunction. J Sex Med. 2006;3(Suppl):52.
30. Perelman MA. Why the sexual tipping point® model? Curr Sex Health Reports. 2016;8(1), 39–46. http://doi.org/10.1007/s11930-016-0066-1.
31. Perelman MA. Post-prostatectomy orgasmic response. J Sex Med. 2008;5(1):248–9.
32. Phelps J, Jain A, Monga M. The PsychoedPlusMed approach to erectile dysfunction treatment: the impact of combining a psychoeducational intervention with sildenafil. J Sex Marital Ther. 2004;30(5):305–14.
33. Rosen R. Medical and psychological interventions for erectile dysfunction: toward a combined treatment approach. In: Leiblum S, Rosen R, editors. Principles and practice of sex therapy. 3rd ed. New York, NY: Guilford Press; 2000.
34. Bancroft J, Graham CA, Janssen E, Sanders SA. The dual control model: current status and future directions. J Sex Res. 2009;46(2/3):121–42.
35. Basson R. The female sexual response: a different model. J Sex Marital Ther. 2000;26:51–65.
36. Kaplan H. The sexual desire disorders: dysfunctional regulation of sexual motivation. New York, NY: Brunner/Mazel, Inc; 1995.
37. Metz ME, McCarthy BW. The "good-enough sex" model for couple satisfaction. Sex Relationship Ther. 2007;22(3):351–62.
38. Perelman MA. The sexual tipping point: a mind/body model for sexual medicine. J Sex Med. 2009;6(3):629–32.
39. Pfaus J. Pathways of sexual desire. J Sex Med. 2009;6(6):1506–33.
40. Blonna R, Watter D. Health counseling: a microskills approach. Boston, MA: Jones and Bartlett Publishers; 2005.
41. Perelman MA. The history of sexual medicine. In: Tolman D, Diamond L, editors. APA handbook of sexuality and psychology. Washington, DC: American Psychiatric Association Press; 2013.
42. Risen CB. Listening to sexual stories. In: Levine SB, Risen CB, Althof SE, editors. Handbook of clinical sexuality for mental health professionals. 2nd ed. New York, NY: Routledge; 2010.
43. Annon J. The behavioral treatment of sexual problems: brief therapy. New York, NY: Harper and Row; 1976.
44. Marino G. Kierkegaard on the couch. The New York Times [Internet]. 2009. http://happydays.blogs.nytimes.com. Accessed 28 Oct 2009.
45. Watter DN. The medicalization of sex therapy: better living through chemistry? J Ethics Mental Health. 2012;7(Suppl):1–4. http://www.jemh.ca. Accessed 12 Sept 2015.
46. Szasz TS. Sex by prescription. New York, NY: Penguin; 1980.
47. Tiefer L. Sex is not a natural act and other essays. Boulder, CO: Westview Press; 1995.
48. Watter DN. Ethics and sex therapy: a neglected dimension. In: Kleinplatz PJ, editor. New directions in sex therapy: innovations and alternatives. 2nd ed. New York, NY: Routledge; 2012.
49. Miner MM, Perelman MA. A psychological perspective on male rejuvenation. Fertil Steril. 2013;99(7):1803–6.
50. Naccarato A, Wolf G, Caron F, Ferreira U, Denardi F. Quality of life and sexual health in survivors of prostate cancer undergoing radical prostatectomy: a preliminary result after 10 years of surgery. Paper presented at the 4th international consultation on sexual medicine; 2015.
51. Katz A. Prostate cancer and the man you love: supporting and caring for your partner. New York, NY: Rowman and Littlefield Publisher; 2012.
52. McCarthy BW, Metz ME. Men's sexual health: fitness for satisfying sex. New York, NY: Routledge; 2008.
53. Hall KSK, Graham CA, editors. The cultural context of sexual pleasure and problems: psychotherapy with diverse clients. New York, NY: Routledge; 2013.
54. Nichols M. Therapy with LGBTQ clients: working with sex and gender variance from a queer theory model. In: Binik YM, Hall KSK, editors. Principles and practice of sex therapy. 5th ed. New York, NY: Guilford Press; 2014.
55. Sandfort TGM, de Keizer M. Sexual problems in gay men: an overview of empirical research. Annu Rev Sex Res. 2001;12:93–120.
56. Hart TA, Wolitski RJ, Purcell DW. Sexual behavior among HIV-positive men who have sex with men: what's in a label? J Sex Res. 2003;40(2):179–88.
57. Moser C. Health care without shame: a handbook for the sexually diverse and their caregivers. San Francisco, CA: Greenery Press; 1999.

Epidemiology of Erectile Dysfunction and Key Risk Factors

4

Raymond C. Rosen and Varant Kupelian

Background and Overview

Erectile dysfunction is a significant and common medical problem. Epidemiologic surveys in the past 20 years suggest that approximately 30–40 % of men over 40 have ED to one degree or another. Data from the Massachusetts Male Aging Study (MMAS) have shown that ED is a common occurrence among aging men with a prevalence rate of 34.8 % of moderate to complete ED [1]. The disorder is highly age dependent, as the prevalence rises from 2 % for men aged 40–49, 6 % for men aged 50–59, 17 % for men aged 60–69, and 39 % for men aged 70 and older [2]. Recent reports from the National Health and Nutrition Examination Survey (NHANES III) and the Males Attitude Regarding Sexual Health Survey (MARSH) show similar prevalence estimates [3, 4]. NHANES data suggest that Hispanics are more likely to report ED especially at younger ages (<50 years) [3], a pattern not observed in the MARSH study [4].

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The role of aging in ED has been investigated in several studies. In a large national sample of men ($N = 1455$) between the ages of 57 and 85 years of age [5], 37 % of men in the overall sample had problems with ED, increasing to 44 % in the 75–85-year age group. Men were asked whether or not they had "difficulty achieving or maintaining an erection for several months or more during the past year." Of note, 90 % of men with ED reported being bothered by the problem. Fourteen percent of men in the sample reported the use of medications to improve sexual function. As in previous studies, age and diabetes were significant independent risk factors for ED in this study [5], in addition to overall health and well-being. Previously, Laumann et al. [6] had shown that ED increases from 7 % in men under 30–18 % in men aged 50–59. Taken together with the recent findings from the Lindau et al. [5] study, it appears that ED increases about 400-fold from less than 10 % of men under age 30 to almost 50 % of men aged 50 and above. However, we should note that almost 50 % of men aged 50 and above *do not* develop ED, and thus it should not be viewed as a natural or inevitable consequence of aging. The role of medical comorbidities and risk factors has been shown to be increasingly important.

Findings from multiple epidemiological studies have also shown convincingly that ED impacts mood state, interpersonal functioning, and overall quality of life (2–8). ED is associated with a wide range of psychosocial consequences

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and risk factors, such as decreased quality of life (QoL), poor self-esteem, and increased incidence of depression and interpersonal relationship problems [7–10]. Numerous studies have demonstrated that ED can undermine a man's QoL; for example, Jønler et al. [11] have shown that patients with the loss of erectile function within the past year had significantly lower QoL than men without ED. Similarly, in other recent studies, men with a complaint of ED had poorer QoL than age-matched men from the general population [12, 13]. QoL was also shown to be impaired in men with ED and diabetes [14] who showed significantly higher levels of diabetes-specific health distress, worse psychological adaptation to and acceptance of diabetes, and a less satisfactory sexual life. Moreover, these men were more easily frustrated and discouraged by their diabetes, which translated into worse metabolic control and higher levels of depressive symptoms. Although not a life-threatening condition, ED is thought to have a profound effect on the quality of life of aging men [15]. Moreover, ED is viewed increasingly as a harbinger or signal of future cardiovascular events.

The role of comorbidities has been recognized since the MMAS and other early epidemiologic findings [1]. Among the major comorbidities and risk factors for ED are diabetes, depression, and cardiovascular disease [8, 16–20]. This classic trio of risk factors has been implicated in multiple epidemiologic studies, across multiple populations and research settings. Medications for diabetes, hypertension, cardiovascular disease, and depression may also cause erectile difficulties [21]. In addition, there is a substantially higher prevalence of erectile dysfunction among men who have undergone radiation or surgery for prostate cancer or who have a lower spinal cord injury or other neurological diseases (e.g., Parkinson's disease, multiple sclerosis). Lifestyle factors, including smoking, alcohol consumption, and sedentary behavior, are additional risk factors [20]. Despite its increasing prevalence among older men, erectile dysfunction is not considered a normal or inevitable part of the aging process. It is rarely (in fewer than 5 % of cases) due to aging-related hypogonadism, although the relationship between erectile dysfunction and age-related declines in androgen remains controversial.

One recent review [22] highlighted four major areas of epidemiologic contribution: (1) ED is highly prevalent in aging men, affecting approximately 50 % of all men older than 60. For many men, ED manifests in their 40s and 50s, increasing in frequency and severity after age 60 [1, 23–25]. (2) The degree of bother associated with ED is inversely related to aging, as men older than 70 typically report a somewhat lower degree of bother than their younger counterparts. The level of bother and treatment seeking is typically higher in younger and middle aged, compared to older men [14, 19, 26]. (3) The prevalence and incidence of ED are highly correlated with the presence of known risk factors and comorbidities, which have a linearly increasing effect on ED. Specifically, cardiovascular comorbidities (e.g., hypertension, hypercholesterolemia), diabetes mellitus, and the metabolic syndrome have all been associated with the increasing prevalence of ED in multiple cross-sectional and longitudinal studies [10, 14, 27, 28]. Additionally, depression and lower urinary tract symptoms (LUTS) have been associated with ED in a number of recent studies [13, 29–31]. (4) Lifestyle factors, including smoking, obesity, and exercise, are also significant predictors of ED [10, 32, 33].

Is ED predictive of cardiovascular disease (i.e., a sentinel or harbinger of future cardiovascular events)? Accumulating evidence of a pathophysiologic and epidemiologic association between ED and cardiovascular risk factors and disease has led to the hypothesis of ED as a possible marker for CVD [17, 34–38]. The association between cardiovascular risk factors and ED was first demonstrated longitudinally in the MMAS [28] and has been subsequently confirmed in other large epidemiologic studies [10, 39, 40]. The hypothesized pathophysiological link between ED and CVD is firmly based in a growing body of epidemiological data and could have profound public health significance. The onset of ED (to the degree that it reflects systemic arterial compromise, as has been repeatedly

demonstrated) may be interpreted as a sentinel of subclinical cardiovascular disease.

Several studies have documented a strong cross-sectional association between ED and clinical manifestations of CVD. Smoking, physical activity, hypertension, hypercholesterolemia, and diabetes, which are all related to endothelial injury leading to atherosclerosis, are important risk factors for both ED and CVD [3, 4, 18, 32, 41–51]. In the MMAS study, cigarette smoking (both active and passive) and unfavorable lipid levels were associated with ED [1]. Additional studies have shown a dose–response relationship between pack-years of smoking and risk of ED [41, 49]. Obesity and physical activity have also been related to ED. Esposito et al. have shown that weight loss and increased physical activity were associated with improved sexual function in about one third of obese men with ED at baseline [52].

Longitudinal data, from a historical cohort study based on medical records data [53] and from the Prostate Cancer Prevention Trial [54], provide the strongest evidence to date of ED as an *independent predictor of CVD*, with an associated increased risk of CVD similar to the effect of smoking or family history of myocardial infarction. The clinical importance of ED as a marker of CVD has been underscored by the most recent Princeton III Consensus Conference [55] and the International Consultation in Sexual Medicine [56]. Strong recommendations were made by both of these guideline committees for the proactive cardiovascular assessment and specific assessment of cardiovascular risk in *all* men presenting clinically with ED.

While recent data from the Massachusetts Male Aging Study show that addition of ED to the Framingham Risk Score did not result in significant improvement in CV risk prediction in men 40–70 years of age (11 % of men who developed CVD within 10 years were reclassified into a higher risk category, while 6.2 % of men who did not develop CVD were reclassified into higher risk category and ED), ED remained a marker of increased CVD risk independent of the FRS and established CVD risk factors [57]. However, change in CV risk prediction with addition of ED could not be assessed in men younger than 40 years or age. Data from the Olmsted County Study from January, 1996 to December, 2005 consisting of a sample of 1400 community-dwelling men with regular sexual partners showed a highly significant three-way interaction between age, ED, and new-incident coronary artery disease (Inman et al. [2]). Specifically, the rate of new-incident coronary artery disease nearly doubled in the men with ED compared to the men without ED, controlling in the model for age and effects of other comorbidities. Controlling for the effects of other comorbidities only slightly decreased the strength of this relationship (OR = 1.8; 1.2–2.6). In the 70 and older age group, the unadjusted odds ratio was 5.5 (3.4–9.7). Similarly, ED was strongly predictive of subsequent cardiovascular events among younger men in a study from Western Australia comparing incidence of CV events in a cohort of 1660 men with incidence in the general male population [58]. While recent data from the Massachusetts Male Aging Study show that addition of ED to the Framingham Risk Score resulted only in a slight improvement in CV risk prediction in men 40–70 years of age, this latest study provides additional, independent confirmation in a well-characterized longitudinal sample of men of the strong association between ED and clinically relevant aspects of cardiovascular health, including new-incident coronary artery disease. Undoubtedly, clinicians should routinely enquire about sexual function and ED in all men over 40, including the severity of ED, as severity is associated with greater risk of CVD [59, 60], and symptomatic men should be proactively investigated for their overall cardiovascular health, including any symptoms of angina or coronary artery disease.

In reviewing results from multiple epidemiological studies, we can conclude for the importance of medical comorbidities (e.g., hypertension, diabetes, lower urinary tract symptoms) and lifestyle factors (e.g., obesity, sedentary lifestyle) as key determinants of ED. By assessing the impact of specific risk factors and comorbidities, we aim to identify suitable targets for future treatment and prevention. Current

medical or surgical therapies for ED may be viewed as symptomatic or palliative treatments [26], which fail to address the underlying pathophysiological mechanisms involved [61, 62]. Findings from population-based studies should be used to guide clinical prevention or education efforts. These should be directed to those patient groups or individuals most likely to benefit from early intervention (e.g., men without major illnesses or comorbidities) [33].

ED Progression and Remission

What factors account for early onset and progression of ED in some men, but not others? Despite the overall association with aging, a number of older men in their eighth and ninth decades continue to enjoy sexual activity and adequate penile erections [20, 63, 64].

The increased incidence of ED and progressive decline in testosterone levels in aging men is well documented [7, 8, 23, 65]. Recent findings, in particular, from the MMAS study have demonstrated the remission of ED in a significant proportion of men over time, even without specific intervention or the use of oral medications or other ED treatments [66]. In analyzed data from the MMAS to investigate the natural history of ED, including both progression and remission, 401 men of the original MMAS sample were followed who reported minimal, moderate, or complete ED at T1 (1988–1992) [66]. These men were eligible for remission, defined as a lessening of severity by at least one category of ED from T1 to T2 (1996–1998). Of the 401 men included in this analysis (Fig. 4.1), 141 subjects (35 %) exhibited ED remission by T2 (95 % CI: 30 %, 40 %). Of 323 subjects with minimal or moderate ED at T1, 107 (33 %) exhibited ED progression (95 % CI: 28 %, 38 %). The proportion of men with ED experiencing progression, remission, and remaining stable is roughly equivalent (Fig. 4.1) [9, 66]. Age and BMI were associated in this analysis with both progression and remission, while smoking and self-assessed health status were associated with progression only. These observations (which predate development of PDE-5s) suggest that the likelihood of natural remission of ED and its symptoms is more common than previously believed. Furthermore, it provides positive support for the use of lifestyle modification or other nonpharmacological treatments for ED. These new findings have important clinical implications, particularly given the fact that increasing numbers of patients prefer nonpharmacological means of treatment.

ED Findings from the Boston Area Community Health Survey (Fig. 4.2)

Recent findings from the Boston Area Community Health (BACH) Survey have provided further evidence of the association of ED with prevalent comorbid conditions and modifiable risk factors in a large population-based epidemiologic study, as well as new insights on the role of socioeconomic status (SES) and race/ethnic disparities in ED, as well as the complex interaction between ED, chronic illnesses, and prescription medication use.

BACH is a community-based epidemiologic study of a broad range of urologic symptoms in a random sample of over 5500 adults, including 2301 men age 30–79 years. The BACH study used a multistage-stratified design to recruit approximately equal numbers by age decade, gender, and race/ethnicity, resulting in a population representative, diverse sample. Multidisciplinary data collected through an extensive in-home interview include a wide range of covariates, including anthropometric and blood pressure measurements, venous blood sample collection, self-reported medical history, sociodemographic characteristics, and lifestyle and psychosocial factors as well as administration of an extensive sexual questionnaire, including the International Index of Erectile Function (IIEF-5). Medication use was collected using a combination of drug inventory and self-report with a prompt by indication [67].

Consistent with findings from previous studies, results of the BACH study show a strong association between ED and major chronic illnesses, such as heart disease, diabetes, and

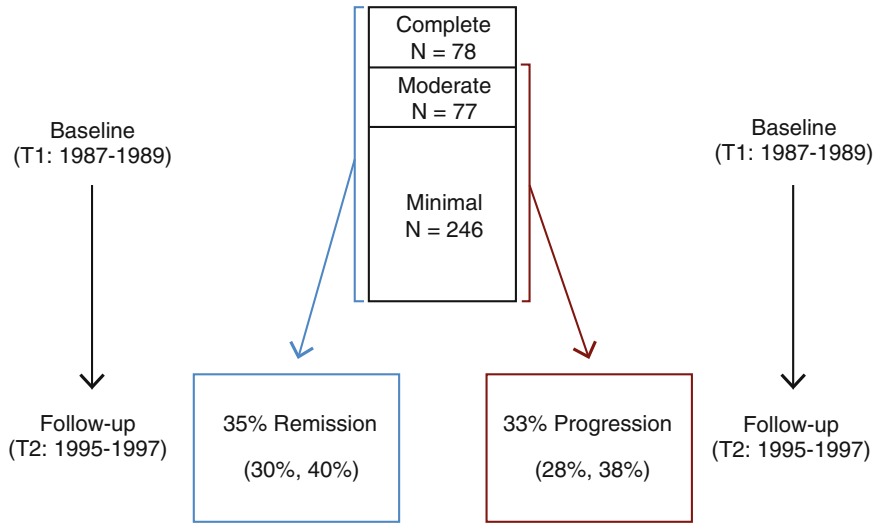

Fig. 4.1 MMAS: Progression and remission of ED with time (1987–1997); proportion (%) and (95% confidence intervals) (Used with permission from Travison TG, Shabsigh R, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The natural progression and remission of erectile dysfunction: Results from the Massachusetts Male Aging Study. Journal of Urology 2007; 177(1), 241–246. Discussion 246)

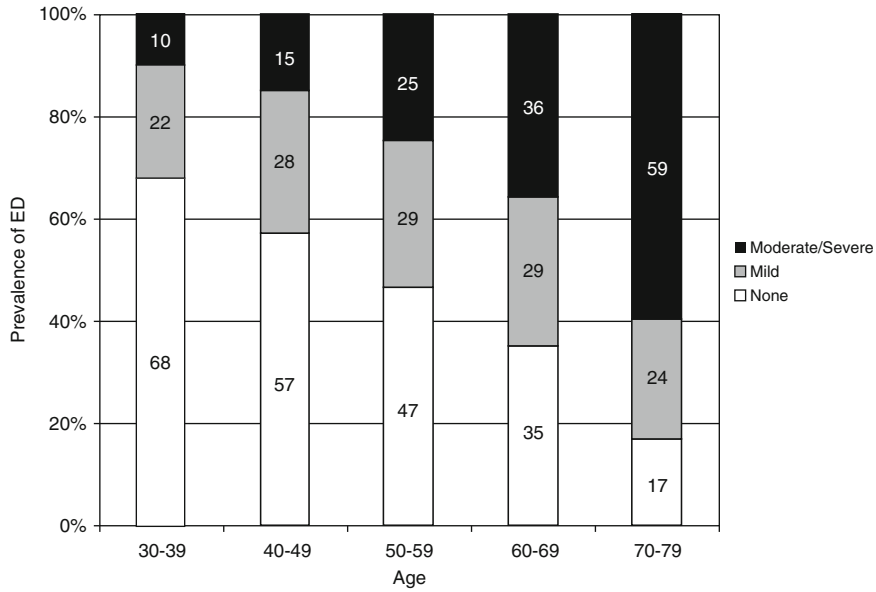

Fig. 4.2 Prevalence of erectile dysfunction by age. Boston Area Community Health (BACH) Study 2002–2005

depression with an approximately twofold increase in risk of ED [68, 69]. A comparable association between hypertension and ED disappeared only after adjusting for heart disease and diabetes. While the association between overall obesity, assessed by BMI and ED, was weak, a much stronger association was observed when considering abdominal obesity measured by waist-to-hip ratio. Similar to the association of ED and hypertension, the effect of abdominal

obesity was nonsignificant only after controlling diabetes and heart disease. Overall, these results were consistent across race/ethnic groups, with only minor observed differences between groups.

Recent longitudinal analyses of the BACH Survey, using data from two follow-up assessments approximately 5 and 10 years following baseline, investigated the association between change in ED status and cardiovascular risk assessed by the Framingham Risk Score [70]. Results suggest that both transient and persistent ED are associated with an increase CVD risk and also with an increase in the FRS score, particularly in men <50 years of age. As endothelial dysfunction has been hypothesized as a plausible mechanism linking ED and cardiovascular disease, the association of ED with macrovascular and microvascular endothelial dysfunction assessed by ultrasound studies was investigated in a subset of 389 men from the BACH Survey. Results show a nonsignificant difference in flow-mediated dilation, a measure of macrovascular disease, between men and without ED. However, hyperemic velocity was lower in men with ED compared to men without ED (mean of 97.1 (SE = 2.5) cm/s vs. 106.0 (SE = 1.6) cm/s, $p = 0.003$). This association remained statistically significant after adjusting for traditional cardiovascular risk factors, suggesting that microvascular endothelial dysfunction is a potential independent contributor to ED and an underlying mechanism linking ED and CVD [71].

Results from the BACH study also contribute to the growing body of epidemiologic and basic science support for an association between ED and LUTS. This association was first reported by the author in a large, multinational study of more than 11,000 men in seven countries (MSAM-7) [29]. In this study, age, LUTS, and male sexual function, including erectile function, orgasmic ability, and sexual desire, were strongly associated, after controlling for relevant covariates to LUTS prevalence and severity [29]. See Fig. 4.3.

Most recently, Egan [72] reported that ED and BPH overlap significantly in a large nationally representative sample of men in the NHANES 2001–2004 Surveys. Of 393 men with defined BPH in this sample, more than half (57.8 %) had coexistent ED, confirming the moderately strong co-occurrence of the conditions across a broad spectrum of men ($p < 0.0001$). Coexisting ED/BPH occurred in 10.6 % of the NHANES male cohort, while 24.4 and 7.7 % reported ED and BPH alone. After age 60, the odds of reporting ED, BPH, or ED/BPH compared to men who had neither condition almost tripled per decade of increasing age, corresponding to marked prevalence increases with increasing age. Notably, PSA was a significant predictor also, as unadjusted odds of ED/BPH vs. no disease increased 1.3 times per PSA unit (ng/mL) increase. Other correlated factors for ED/BPH included BMI (OR = 2.5), increased use of antidiabetic medications (OR = 2.9), and four or more healthcare visits per year (OR = 3.5) compared to men without either condition [72].

Using data from the BACH study, we further investigated the contribution of urinary incontinence and prostatitis which are common voiding symptoms not included in the AUA symptom index. The observed association in BACH between ED and LUTS, both conditions with increasing prevalence in aging men, is consistent with findings from previous studies [29]. BACH data show that this association is largely due to the association with nocturia, among common symptoms of LUTS, and also with symptoms of urinary incontinence and prostatitis, with results again consistent across race/ethnic groups [73]. Similar results were recently observed when investigating the association between urinary symptoms and low sexual desire and sexual inactivity [74].

In addition to the role of comorbid medical conditions, BACH findings also provide support for the contribution of potentially modifiable behavioral risk factors, such as physical activity, smoking, and alcohol consumption in their effects on ED. Results show a weak association between alcohol consumption and ED, in particular, with no evidence for a linear trend, as moderate alcohol consumption was associated with a slight decreased in risk, while increased amounts were associated with very slightly higher risk of

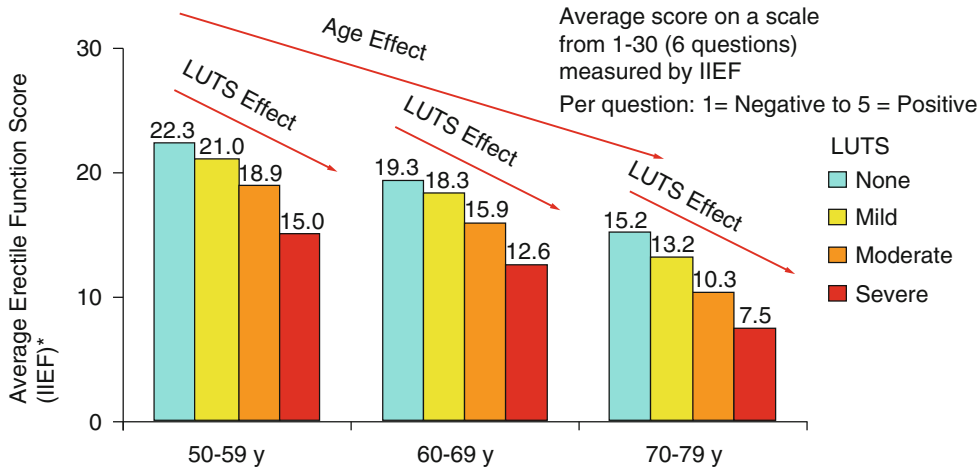

Fig. 4.3 Shows average score for erectile function (as measured by IIEF) in each age group among men without LUTS (*blue bars*). As expected, a clear decline in erectile function with increasing age can be observed (*age effect*) (Data from Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E, O'Leary MP, Puppo P, Robertson C, Giuliano F, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol 2003; 44:637–649)

ED. On the other hand, a *clear trend* in decreased risk of ED was observed with increased physical activity [69]. BACH data also provide further evidence of the increased risk of ED associated with smoking with a strong dose–response pattern in between duration and intensity of smoking and increased risk of ED with a significant increase in ED risk with exposure to 20 pack-years or more. BACH data also permit the assessment of the impact of exposure to second-hand smoke (passive smoking) and show a moderate, statistically nonsignificant, increase in the risk of ED comparable to the effect observed for 10–19 years of smoking [41]. These results highlight the importance and opportunity for the intervention on modifiable behavioral factors, such as *smoking cessation* and increased *physical activity* in prevention or improvement in erectile function as well as the possibility of adverse effects of long-term chronic exposure to passive smoking [41].

Although differences in prevalence and risk of ED by race/ethnicity have been reported previously, findings have not been consistent and have seldom taken into account the separate contributions of SES and other background variables to apparent race/ethnic disparities [3, 6, 75]. The strength of the BACH study is the race/ethnic and socioeconomic diversity of the sample and balance, with the SES index calculated as weighted sum education and income and categorized as low, middle, and high SES based on the 25th and 75th percentiles of the distribution of the SES index. Prevalence estimates of ED by race/ethnicity show that ED is more common among Black and Hispanic men with a prevalence rate of 25 % compared to a prevalence rate of 18 % among White men. These differences persisted after adjusting for age, comorbid conditions, and lifestyle factors. However, there were significant differences in the SES composition of the three race/ethnic groups, and differences in ED prevalence were even larger across SES categories, with a prevalence rate of 36 % for the low SES category, in particular. Once we controlled SES in the subsequent multivariate analyses, the differences between the race/ethnic groups were lost (Fig. 4.4), while the low SES group remained at more than twofold increased risk of ED, independent of the effects of age, comorbid medical conditions (heart disease, diabetes, depression), and lifestyle risk factors (smoking, physical activity). These findings point to a need for further research to understand the potential role of SES-dependent factors and variables—such as

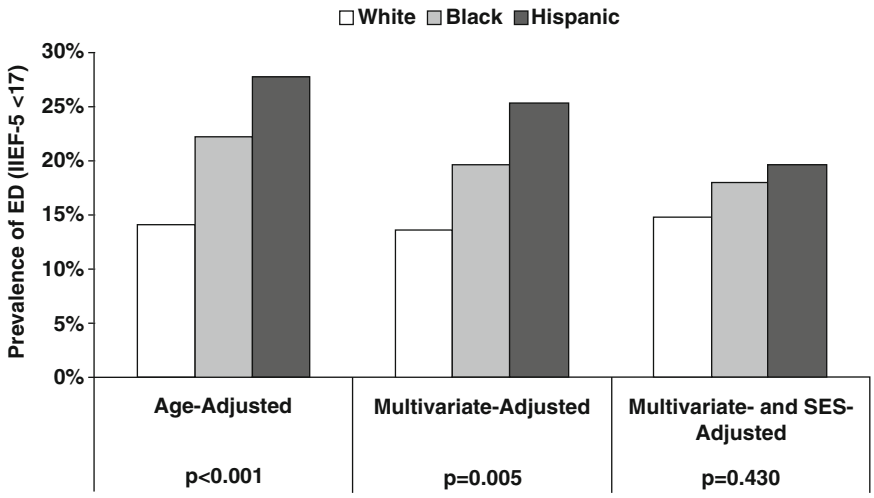

Fig. 4.4 Association of race/ethnicity and erectile dysfunction disappears after adjusting for socioeconomic status

occupational health, nutrition, and access to healthcare—that may contribute to the increased risk of ED in our low SES group.

Inventory-based medications data collected in the BACH study also present the opportunity to investigate effects of common medications on ED. An analysis of lipid-lowering medications, including statins and nonstatin antilipemics, shows a complex interaction between the use of medications and the presence of comorbid chronic illnesses and age. An association between statin use and increased risk of ED was observed only among younger men (age <55 years) who had diabetes or cardiovascular disease, while the association essentially disappeared or was obscured in older men in the BACH sample. Additionally, no association was seen in our cohort between untreated hyperlipidemia and ED in multivariate analyses. These findings suggest that lipid-lowering agents may be associated with some increased risk of ED in some men. However, this potential adverse effect of statins and other antilipemic medications should be weighed against the well-established benefits of lipid-lowering therapy in the reduction of major coronary events and mortality. Further research is needed to determine whether other classes of medication contribute to interaction with lipids and resulting changes in prevalence rates of ED across samples [21].

Discussion

Conceptual and methodological issues need to be addressed. First, the definition and measurement of ED vary from study to study. All definitions of ED, however, are based on patients' self-report, which is typically assessed by single-item scales or questionnaire measures [76–80]. Some differences are evident among these scales, although studies show overall concordance in the prevalence rates and association with well-known comorbidities and risk factors. Early landmark studies, such as MMAS and National Health and Social Life Survey (NHSLS) used single-item scales, which assessed erection difficulties over several months or in the past year [76, 77]. Subsequent studies used 5- or 15-item versions of the IIEF, a multidimensional, self-report scale that assesses male sexual function over a 4-week period [80]. Single-item instruments have the advantage of high completion rates and low patient burden. On the other hand, multidimensional scales provide broader and more complete assessment of disease severity. Despite such differences, largely similar results have been obtained across studies using these different measures.

A second and potentially more challenging issue concerns the complex and often bidirec-

tional interactions between variables. For example, depression may be a cause or a consequence of ED in many studies [8, 9, 31, 81]. These studies support a direct association between ED and mood. In other studies, the causal relationships among the major risk factors for ED are less evident. Biomedical, psychosocial, and lifestyle factors may interact in complex ways. Separating the effects of one risk factor or comorbidity from another and determining the direction of causality among these factors can be difficult if not impossible to ascertain in cross-sectional studies alone [20, 63, 79, 82]. More research is needed to elucidate these associations.

The increased evidence of a link between ED and CVD with the potential for ED to serve as a sentinel marker of subclinical vascular disease has led to an increased awareness of ED as a "barometer" of vascular health and the early opportunity for primary prevention in at-risk men. The second Princeton Consensus Conference has called for the routine assessment of cardiovascular risk in all ED patients and subsequent classification of ED patients into low, moderate, or high risk of CVD and recommendation for aggressive lifestyle modification in patients with ED and CV risk factors [77]. However, further understanding is needed of the link between endothelial dysfunction and ED and the specific role of endothelial dysfunction in the progression and remission of ED to (1) refine our understanding of pathophysiological processes of ED in human subjects; (2) improve the identification of ED patients at higher risk of CVD who would benefit most from preventive interventions, such as statin therapy, perioperative beta blocker therapy, etc.; and (3) establish the primacy of endothelial dysfunction in ED incidence and progression and relationship to other predictors.

References

1. 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(1):54–61.
2. Inman BA, Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc. 2009;84(2):108–13.
3. Saigal CS, Wessells H, Pace J, Schonlau M, Wilt TJ. Predictors and prevalence of erectile dysfunction in a racially diverse population. Arch Intern Med. 2006;166(2):207–12.
4. Laumann EO, Paik A, Glasser DB, et al. A cross-national study of subjective sexual well-being among older women and men: findings from the global study of sexual attitudes and behaviors. Arch Sex Behav. 2006;35(2):145–61.
5. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762–74.
6. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537–44.
7. Andersson KE, Wagner G. Physiology of penile erection. Physiol Rev. 1995;75:191–236.
8. Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med. 1998;60(4):458–65.
9. Araujo AB, Johannes CB, Feldman HA, Derby CA, McKinlay JB. Relation between psychosocial risk factors and incident erectile dysfunction: prospective results from the Massachusetts Male Aging Study. Am J Epidemiol. 2000;152(6):533–41.
10. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med. 2003;139(3):161–8.
11. Barrett-Connor E. Heart disease factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. Am J Cardiol. 2009;57(6):1041–4.
12. Blanker MH, Bosch JL, Groeneveld FP, et al. Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: prevalence, concern, and relation to sexual activity. Urology. 2001;57(4):763–8.
13. Blanker MH, Bohnen AM, Groeneveld FP, et al. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. J Am Geriatr Soc. 2001;49(4):436–42.
14. 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(6):305–11.
15. Krane RJ, Goldstein I, Saenz de Tejada I. Impotence. N Engl J Med. 1989;321(24):1648–59.
16. Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. Urology. 2004;64(6):1196–201.

17. Montorsi P, Ravagnani PM, Galli M, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J. 2006;27(22):2632–9.
18. Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. Eur Urol. 2005;47(1):80–5. Discussion 85–86.
19. Holden CA, McLachlan RI, Pitts M, et al. Men in Australia Telephone Survey (MATeS): a national survey of the reproductive health and concerns of middle-aged and older Australian men. Lancet. 2005; 366(9481):218–24.
20. Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin. 2004;20(5):607–17.
21. Hall SA, Kupelian V, Rosen RC, et al. Is hyperlipidemia or its treatment associated with erectile dysfunction? Results from the Boston Area Community Health (BACH) Survey. J Sex Med. 2009; 6(5):1402–13.
22. Rosen RC, Wing R, Schneider S, Gendrano III N. Epidemiology of erectile dysfunction: the role of medical comorbidities and lifestyle factors. Urol Clin North Am. 2005;32(4):403–17.
23. 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. J Urol. 2000;163(2):460–3.
24. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, Rodriguez-Vela L, Jimenez-Cruz JF, Burgos-Rodriguez R. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. J Urol. 2001;166(2):569–74. Discussion 574–565.
25. Pinnock CB, Stapleton AM, Marshall VR. Erectile dysfunction in the community: a prevalence study. Med J Aust. 1999;171(7):353–7.
26. Fisher WA, Rosen RC, Eardley I, et al. The multinational Men's Attitudes to Life Events and Sexuality (MALES) study phase II: understanding PDE5 inhibitor treatment seeking patterns, among men with erectile dysfunction. J Sex Med. 2004;1(2):150–60.
27. Esposito K, Giugliano D. Obesity, the metabolic syndrome, and sexual dysfunction. Int J Impot Res. 2005;17(5):391–8.
28. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: Prospective results from the Massachusetts male aging study. Prev Med. 2000;30(4):328–38.
29. Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol. 2003;44(6):637–49.
30. Rosen RC, Giuliano F, Carson CC. Sexual dysfunction and lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Eur Urol. 2005;47(6):824–37.
31. Rosen RC, Seidman SN, Menza MA, et al. Quality of life, mood, and sexual function: a path analytic model of treatment effects in men with erectile dysfunction and depressive symptoms. Int J Impot Res. 2004; 16(4):334–40.
32. 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(2):302–6.
33. Nicolosi A, Glasser DB, Moreira ED, Villa M. Prevalence of erectile dysfunction and associated factors among men without concomitant diseases: a population study. Int J Impot Res. 2003;15(4):253–7.
34. Kostis JB, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the second Princeton consensus conference). Am J Cardiol. 2005;96(2):313–21.
35. Russell ST, Khandheria BK, Nehra A. Erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2004;79(6):782–94.
36. Solomon H, DeBusk RF, Jackson G. Erectile dysfunction: the need to be evaluated, the right to be treated. Am Heart J. 2005;150(4):620–6.
37. Montorsi P, Montorsi F, Schulman C. Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? Eur Urol. 2003;44(3):352–4.
38. Billups KL. Sexual dysfunction and cardiovascular disease: integrative concepts and strategies. Am J Cardiol. 2005;96(12B):57M–61.
39. Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. J Am Coll Cardiol. 2004;43(8):1405–11.
40. Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later (the Rancho Bernardo Study). Am J Cardiol. 2005;96(12B): 3M–7.
41. Kupelian V, Link CL, McKinlay JB. Association between smoking, passive smoking, and erectile dysfunction: results from the Boston Area Community Health (BACH) Survey. Eur Urol. 2007;52(2): 416–22.
42. Klein R, Klein BE, Lee KE, Moss SE, Cruickshanks KJ. Prevalence of self-reported erectile dysfunction in people with long-term IDDM. Diabetes Care. 1996;19(2):135–41.
43. Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? Am J Epidemiol. 1994;140(11):1003–8.
44. Muller SC, el-Damanhoury H, Ruth J, Lue TF. Hypertension and impotence. Eur Urol. 1991; 19(1):29–34.
45. Rosen MP, Greenfield AJ, Walker TG, et al. Cigarette smoking: an independent risk factor for atherosclerosis

in the hypogastric-cavernous arterial bed of men with arteriogenic impotence. J Urol. 1991;145(4):759–63.
46. Shabsigh R, Fishman IJ, Schum C, Dunn JK. Cigarette smoking and other vascular risk factors in vasculogenic impotence. Urology. 1991;38(3):227–31.
47. Wei M, Macera CA, Davis DR, Hornung CA, Nankin HR, Blair SN. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. Am J Epidemiol. 1994;140(10):930–7.
48. Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. Lancet. 1985;1(8422):181–4.
49. Gades NM, Nehra A, Jacobson DJ, et al. Association between smoking and erectile dysfunction: a population-based study. Am J Epidemiol. 2005; 161(4):346–51.
50. Jeremy JY, Mikhailidis DP. Cigarette smoking and erectile dysfunction. J R Soc Promot Health. 1998;118(3):151–5.
51. Hatzichristou DG, Goldstein I, Quist WC. Preexisting vascular pathology in donor and recipient vessels during penile microvascular arterial bypass surgery. J Urol. 1994;151(5):1217–24.
52. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 2004; 291(24):2978–84.
53. Frantzen J, Speel TG, Kiemeney LA, Meuleman EJ. Cardiovascular risk among men seeking help for erectile dysfunction. Ann Epidemiol. 2006;16(2):85–90.
54. Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. JAMA. 2005;294(23):2996–3002.
55. Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, Carson CC, Cunningham GR, Ganz P, Goldstein I, Guay AT, Hackett G, Kloner RA, Kostis J, Montorsi P, Ramsey M, Rosen R, Sadovsky R, Seftel AD, Shabsigh R, Vlachopoulos C, Wu FC. The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87(8):766–78.
56. Lue TF, Giuliano F, Montorsi F, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2004;1(1):6–23.
57. Araujo A, Hall SA, Ganz P, et al. Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? J Am Coll Cardiol. 2010;55:350–6.
58. Chew K, Finn J, Stuckey B, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. J Sex Med. 2010;7:192–202.
59. Hall SA, Shackelton R, Rosen RC, et al. Sexual activity, erectile dysfunction, and incident cardiovascular events. Am J Cardiol. 2010;105:192–7.
60. Salem S, Abdi S, Abdolrasoul A, et al. Erectile dysfunction severity as a risk predictor for coronary artery disease. J Sex Med. 2009;6:3425–32.
61. Ganz P. Erectile dysfunction: pathophysiological mechanisms pointing to underlying cardiovascular disease. Am J Cardiol. 2005;96(12B):8M–12.
62. Jackson G. Erectile dysfunction and cardiovascular disease. Int J Clin Pract. 1999;53(5):363–8.
63. Laumann EO, Nicolosi A, Glasser DB, et al. Sexual problems among women and men aged 40–80 y: Prevalence and correlates identified in the global study of sexual attitudes and behaviors. Int J Impot Res. 2005;17(1):39–57.
64. Nicolosi A, Glasser DB, Kim SC, Marumo K, Laumann EO. Sexual behavior and dysfunction and help-seeking patterns in adults aged 40–80 years in the urban population of Asian countries. Br J Urol Int. 2005;15:253–7.
65. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87(2):589–98.
66. Travison TG, Shabsigh R, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The natural progression and remission of erectile dysfunction: results from the Massachusetts Male Aging Study. J Urol. 2007;177(1):241–6. Discussion 246.
67. McKinlay JB, Link CL. Measuring the urologic iceberg: design and implementation of the Boston Area Community Health (BACH) Survey. Eur Urol. 2007;52(2):389–96.
68. Fitzgerald MP, Link CL, Litman HJ, Travison TG, McKinlay JB. Beyond the lower urinary tract: the association of urologic and sexual symptoms with common illnesses. Eur Urol. 2007;52(2):407–15.
69. Kupelian V, Link CL, Rosen RC, McKinlay JB. Socioeconomic status, not race/ethnicity, contributes to variation in the prevalence of erectile dysfunction: results from the Boston Area Community Health (BACH) Survey. J Sex Med. 2008;5(6):1325–33.
70. Fang SC, Rosen RC, Vita JA, Ganz P, Kupelian V. Changes in erectile dysfunction over time in relation to Framingham cardiovascular risk in the Boston Area Community Health (BACH) Survey. J Sex Med. 2015;12(1):100–8.
71. Gerber RE, Vita JA, Ganz P, et al. Peripheral microvascular dysfunction and erectile dysfunction. J Urol. 2015;193:612–7.
72. Egan KB, Burnett AL, McVary KT, Ni X, Suh M, Wong DG, Rosen RC. The co-occurring syndrome – co-existing ED and BPH and their clinical correlates in aging men: results from the National Health and Nutrition Examination Survey. Urology. 2015;86(3):570–80.
73. Brookes ST, Link CL, Donovan JL, McKinlay JB. Relationship between lower urinary tract symptoms and erectile dysfunction: results from the Boston Area Community Health Survey. J Urol. 2008;179(1):250–5. Discussion 255.
74. Rosen RC, Link CL, O'Leary MP, Giuliano F, Aiyer LP, Mollon P. Lower urinary tract symptoms and sex-

ual health: the role of gender, lifestyle and medical comorbidities. BJU Int. 2009;103 Suppl 3:42–7.
75. Laumann EO, West S, Glasser D, Carson C, Rosen R, Kang JH. Prevalence and correlates of erectile dysfunction by race and ethnicity among men aged 40 or older in the United States: from the male attitudes regarding sexual health survey. J Sex Med. 2007;4(1):57–65.
76. Derby CA, Araujo AB, Johannes CB, Feldman HA, McKinlay JB. Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging Study. Int J Impot Res. 2000;12(4):197–204.
77. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Construction of a surrogate variable for impotence in the Massachusetts Male Aging Study. J Clin Epidemiol. 1994;47(5):457–67.
78. 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:S60–4.
79. Prins J, Blanker MH, Bohnen AM, Thomas S, Bosch JL. Prevalence of erectile dysfunction: a systematic review of population-based studies. Int J Impot Res. 2002;14(6):422–32.
80. 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(6):822–30.
81. Shabsigh R, Klein LT, Seidman S, Kaplan SA, Lehrhoff BJ, Ritter JS. Increased incidence of depressive symptoms in men with erectile dysfunction. Urology. 1998;52(5):848–52.
82. Nicolosi A, Moreira ED, Jr Shirai M, Bin Mohd Tambi MI, Glasser DB. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology. 2003;61(1):201–6.

Erectile Dysfunction: Etiology and Risk Factors

5

Alexander W. Pastuszak and Mohit Khera

Introduction

Recent studies have shown that sex is a significant part of life for aging men and women, with up to 90 % of men and women 70–90 years old engaging in some form of sexual activity [1, 2]. In the USA, the most common male sexual difficulty is erectile dysfunction (ED), occurring in up to 43 % of men [2]. ED is defined as the persistent inability to achieve or maintain penile erection satisfactory for sexual performance [3]. Male sexual function begins to decline during the fifth decade of life, and this decline affects desire, arousal, erectile function, and ejaculation/orgasm [4–6]. Having ED also negatively affects a man's relationships [7] and emotional and psychological well-being [8, 9]. Given the desire to continue having sex throughout life and the ramifications of ED on physical and psychological health, an understanding of the causes of and risk factors predisposing to ED is essential in the approach to the patient with ED.

The prevalence of ED varies geographically; estimates also fluctuate due to varying study methodologies, questionnaires, and survey tools. The worldwide prevalence of ED is expected to reach 322 million cases by 2025 [10]. In the United States, an estimated 20 million men are currently affected by ED [11]. The majority of affected men are over 40 years old, with only 1–10 % of men under 40 affected by ED [12]. Approximately 2–9 % of men 40–49 years old and 20–40 % of men 60–69 years old are affected. The Massachusetts Male Aging Study (MMAS) was one of the first studies to report on the prevalence of ED, observing ED of any severity in 52 % of men over 40 years old [13]. The rate of moderate to severe ED was observed to increase from 22 to 49 % of men between 40 and 70 years old, suggesting a progressive lesion associated with age. More recently, the National Social Life, Health, and Aging Project (NSHAP) surveyed over 1450 American men to evaluate sexual issues in older adults and reported ED in 31 % of men 57–64 years old and 45 % of men 65–74 years old, with an increased risk of having ED as a function of age (odds ratio (OR) of 1.83 comparing the above age groups) [2]. In men less than 40 years old, ~5 % endorse ED [14]. When comparing ethnic groups, the prevalence of ED is similar, with one study reporting a 22 % ED prevalence in white men, 24 % in black men, and 20 % in Hispanic men over 40 years old [15].

ED has been linked to numerous conditions that can impact morbidity and longevity, including cardiovascular risk factors, diabetes, the

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metabolic syndrome, hypogonadism, benign prostatic hyperplasia, and others, all tied together by a common impact on the vasculature. Numerous other medical conditions, including Peyronie's disease (PD), hypogonadism, lower urinary tract symptoms (LUTS), and others, are also associated with ED. Clinicians are well served to remember that a psychogenic component is integral to virtually all cases of ED and may result from situational or other psychosocial factors. Thus, understanding not only the physiology of normal erectile function, as well as the organic and psychologic factors that impact male erectile function, can result in an optimal approach to men affected by ED.

Physiology of Penile Erection and Detumescence

To better understand the etiology of erectile *dysfunction,* a brief review of the physiology of governing erectile *function* is prudent. Erection is a complex process involving hormonal, vascular, and neural systems. The four stages of normal sexual function in the male include (1) desire, (2) erection, (3) ejaculation, and (4) detumescence, with both the erect and flaccid penile states progressing through initiation and maintenance phases [16]. The pathways and hormones governing penile function are important for both erection and flaccidity, as well as maintenance of penile cavernosal integrity [17, 18].

External stimuli acting through somatic and autonomic pathways initiate erection (reviewed in [11]). Stimuli are sensed by receptors in the penile skin, glans, urethra, and corpus cavernosum, which coalesce into the dorsal nerves of the penis and the pudendal nerve. The pudendal nerve enters the spinal cord at the S2–S4 nerve roots and interfaces with the thalamus and sensory cortex. The process of erection begins with parasympathetic pathway activation resulting in nitric oxide (NO) release from endothelial cells and cavernous nerves. The release of NO causes corporal cavernosal smooth muscle relaxation, reducing peripheral arteriolar resistance and resulting in the inflow of blood [18]. On a molecular level, NO release activates guanylyl cyclase, catalyzing the formation of cyclic guanosine monophosphate (cGMP), which then activates protein kinase G and results in potassium and calcium channel phosphorylation. Phosphorylation of these ion channels results in cellular hyperpolarization, decreasing intracellular calcium levels and causing dissociation of myosin from actin, with the end result being smooth muscle relaxation (reviewed in [19]). Similarly, cyclic adenosine monophosphate (cAMP) also mediates smooth muscle relaxation, but is activated by adenosine, calcitonin gene-related peptides, and prostaglandins rather than by NO [18].

Just as important as penile tumescence is its detumescence, to which several hormonal factors and neurotransmitters contribute. Norepinephrine, phenylephrine, and endothelin are secreted as a result of sympathetic discharge soon after ejaculation and activate phospholipase C, which catalyzes the formation of inositol triphosphate and diacylglycerol [11]. These molecular mediators cause an increase in intracytoplasmic calcium, resulting in smooth muscle contraction. Phosphodiesterase-mediated degradation of cGMP to GMP (PDE5) and cAMP to AMP (PDE4) can also result in detumescence, and an alternate pathway resulting in activation of Rho kinase phosphorylates and inhibits smooth muscle myosin phosphatase, preventing myofilament dephosphorylation and maintaining contraction and the flaccid state [20].

Classification and Etiologic Factors in Erectile Dysfunction

There are two major subtypes of ED—*lifelong*, in which erection is not achieved from the outset of sexual desire, and *acquired*, in which initially normal erectile function and sexual ability are present, which then give way to the onset of ED. Each of these subtypes can have either psychogenic or organic contributors, and both types may require intervention, particularly if lasting more than 3–6 months in light of the link between ED and other conditions that can both worsen ED as well as a man's overall health.

Although often resulting from multiple factors, ED is classified according to its origin: psychogenic; neurologic; vasculogenic, due to other medical or urologic disorders and penile factors; endocrinologic; and drug induced (Table 5.1). We briefly address the various major causes of ED below, subsequently segueing into a deeper discussion of etiologic factors and how they predispose men to developing ED.

Psychogenic ED relates to psychological or interpersonal factors and is mediated by adrenergic inputs [21]. Psychogenic factors that can contribute to ED are often partner related, performance related, or associated with psychological distress [22]. A key psychogenic factor relating to ED is performance anxiety, with the fear of failure during sexual intercourse driving poor erectile function. In contrast with organic etiologies of ED, psychogenic ED is a diagnosis of exclusion, made once organic factors have been ruled out. Clinical clues alerting the physician to the presence of psychogenic ED as a primary etiology of ED include a sudden onset of ED, with intermittency of erectile function sufficient for sexual intercourse, or a situational nature to the erectile problems. Men with psychogenic ED also report good nocturnal erections and difficulty with achieving orgasm, although many are able to achieve orgasm with masturbation [23].

Neurogenic causes of ED relate to neurologic impairment in either the central nervous system or peripheral nerves and in aggregate affect relatively few men. Neurologic disorders frequently related to ED include strokes, dementia, Parkinson's disease, Alzheimer's disease, central nervous system tumors, and spinal cord injury [24]. In addition, lower motor neuron lesions resulting from trauma, pelvic pathology, and pelvic surgery, including radical prostatectomy and cystoprostatectomy, may also result in ED, though recent advances in surgical technique have lowered the incidence of postsurgical ED [25].

ED often results from vascular causes, commonly grouped as arterial insufficiency or venous leak, which together represent the most common organic etiologies of ED. Venous leak ED results

Table 5.1 Etiologies of ED

Psychogenic
Physical and mental health problems
Psychological trauma
Relationship problems/partner dissatisfaction
Family/social pressures
Depression
Organic
Neurologic
Central nervous system—spinal cord injury, multiple sclerosis, stroke
Peripheral nervous system—neuropathy
Vasculogenic
Arterial insufficiency/peripheral arterial disease
Veno-occlusive disease
Hypertension
Trauma
Medical disorders
Hepatic insufficiency
Dyslipidemia
Renal insufficiency
Chronic obstructive pulmonary disease
Sleep apnea
Penile factors
Cavernous fibrosis
Peyronie's disease
Penile fracture
Endocrine
Hypogonadism
Hyperprolactinemia
Diabetes mellitus
Thyroid disorders
Urologic disorders
Benign prostatic hypertrophy
Lower urinary tract symptoms
Drug induced
Antihypertensives
Antidepressants
Antiandrogens
Marijuana
Heroin
Nicotine
Alcohol
Opiates
Cocaine
Iatrogenic
Drug induced
Postoperative
Post-radiation

from increased venous outflow during erection, can inhibit penile tumescence, and is associated with Peyronie's disease, which may limit blood flow due to corporal cavernosal fibrosis. Diabetes mellitus and neurogenic causes of ED may also cause venous leak ED. Arterial insufficiency is often predisposed to by atherosclerosis, hyperlipidemia, hypertension, smoking, diabetes mellitus, and pelvic radiation [26]. Fundamentally, endothelial cell dysfunction is the common factor predisposing to arteriogenic ED, as normal endothelial cell function is protective against arterial cellular dysfunction [27]. ED and cardiovascular disease (CVD) share common risk factors, leading to the concept that vasculogenic ED is a manifestation of vascular disease, and may be the first manifestation of cardiovascular disease [28, 29]. One survey study of over 7500 patients with hypertension and/or diabetes observed ED in nearly 70 % of men with either hypertension or diabetes alone and in 78 % of men with both conditions [30]. A subsequent report evaluating over 2400 men demonstrated that diabetes and hypertension are independently associated with ED, with an age-adjusted odds ratio (OR) of 4.0 in diabetics and 1.58 in hypertensives [31]. Associations between men with high cholesterol (OR 1.63), peripheral vascular disease (OR 2.63), and smoking (OR 2.5) were also observed. The relationship between ED and cardiovascular health is further underscored by improvement in ED symptoms when total and low-density lipoprotein (LDL) cholesterol were lowered using either diet or statin interventions [32].

Androgens play an essential role in maintaining sexual function in both men and women. In men, androgens enhance sexual desire and help to maintain sleep-related erections. Testosterone in particular is important in regulation of NO synthase (NOS) and phosphodiesterase 5 (PDE5) expression in the penis [33]. Testosterone also plays a role in overall erectile function and helps to maintain the fibroelastic properties of penile tissue [34, 35]. Hypogonadism has been linked to cardiovascular morbidity and mortality, with studies finding either an increased or decreased risk of cardiovascular events in men with low testosterone levels, although a consensus on the topic has yet to be reached (reviewed in [36]). Although low serum testosterone levels have not been definitively linked to the presence or severity of ED [37–39], testosterone therapy in men with ED has shown improvement in erectile function in 39 % of men in one study [39], as well as improvements in sexual performance, desire, and motivation in some men [40]. Hyperprolactinemia, often caused by pituitary adenoma, is also associated with low libido and erectile dysfunction, possibly as a result of low testosterone levels that occur with hyperprolactinemia [12, 41]. Diabetes mellitus may also result in ED and is discussed in more detail below.

Drug-induced ED may occur with the use of several drug classes, including antihypertensives, psychotropics, antiandrogens, 5α reductase inhibitors, and digoxin. In addition, marijuana, heroin, cocaine, opiates, nicotine, and alcohol all have negative effects on erectile function as well. Psychotropic drugs and antihypertensives are among the most common drug classes that can lead to ED [42]. Antihypertensive medications that most often result in ED include thiazides and β-blockers, whereas α-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) are the least likely to cause ED [43, 44]. Of psychotropic drugs, the antipsychotics risperidone and olanzapine have the highest likelihood of causing ED [45]. However, antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, are the most common psychotropic drugs associated with ED.

Risk Factors for Erectile Dysfunction

Risk factors for ED are numerous (Table 5.2), although age is the primary risk factor for ED. The prevalence and severity of ED increase with age, with 39 % of men 50 years old having some form of ED, with the rate increasing to 67 % in men by age 70 in the MMAS [12]. These data are substantiated by two other independent, large studies including 2476 Spanish and 1464 Middle Eastern men [31, 46].

Table 5.2 ED risk factors

Age
Coronary artery or peripheral vascular disease
Hypertension
Obesity/sedentary lifestyle
Hyperlipidemia
Trauma or surgery to the pelvis or spine
Diabetes mellitus
Benign prostatic hypertrophy
Lower urinary tract symptoms
Hypogonadism
Peyronie's disease
Endocrine disorders/hypogonadism
Smoking
Depression
Alcohol and drug use
Medications

Cardiovascular Disease and ED

A growing body of evidence has linked ED with cardiovascular disease (CVD) over the past two decades. Significant associations between ED and cardiovascular risk factors including hypertension, dyslipidemia, diabetes mellitus, coronary artery disease (CAD), and the metabolic syndrome have been identified. In a study of 300 men with angiographically documented CAD, 49 % were found to have ED using the International Index of Erectile Function (IIEF), a validated questionnaire for assessment of erectile function [47]. Of the 147 men with both ED and CAD, 67 % reported ED symptoms for 39 months prior to the onset of CAD symptoms. Other studies have corroborated these findings, observing a 2–5-year interval between the onset of ED symptoms and the subsequent onset of cardiovascular symptoms and events [48, 49]. A subsequent prospective study found angiographic, but not clinical, evidence of CAD in nine of 47 (19 %) men with vasculogenic ED [50]. In a landmark study, Inman et al. screened 1400 community men with no evidence of CAD for ED over a 10-year period [51]. The authors found that new CAD developed in 11 % of men during follow-up as a function of age with CAD incidence densities per 1000 person years in men without ED of 0.94 (age 40–49 years), 5.09 (age 50–59 years), 10.72 (age 60–69 years), and 23.30 (age 70 years and older). In contrast, in men with ED, the CAD incidence densities per 1000 person years were 48.52 (age 40–49 years), 27.15 (age 50–59 years), 23.97 (age 60–69 years), and 29.63 (age 70 years and older). Importantly, when ED was found in men <60 years old, it was associated with a significantly higher risk of future cardiac events in comparison with men without ED.

Several meta-analyses have also shown an increased risk of CVD in men with ED, solidifying ED as an independent risk factor for CVD. Vlachopoulos et al. performed a meta-analysis of 14 studies evaluating 92,757 patients with a mean follow-up of 6.1 years, finding that men with ED had a 44 % increased risk for cardiovascular events, a 62 % increased risk for myocardial infarction (MI), a 39 % increased risk for cerebrovascular events, and a 25 % increased risk for all-cause mortality [52]. Dong et al. conducted a smaller meta-analysis of 12 prospective cohort studies encompassing 36,744 men, finding a 48 % increased risk of CVD, a 46 % increased risk of CAD, a 35 % increased risk of stroke, and a 19 % increased risk of all-cause mortality [53]. A third meta-analysis by Guo et al. of 45,558 participants from seven cohort studies calculated an RR of 1.47 for coronary events in men with ED [54]. More importantly, the RR of all-cause mortality in men with ED was determined to be 1.23, correlating ED with future morbidity and death. A study stemming from the Prostate Cancer Prevention Trial (PCPT) demonstrated that ED may be a harbinger of cardiovascular events, with 0.024 cardiovascular events per person year occurring in men with ED compared with 0.015 events in men without ED [55]. Not surprisingly, ED may also be a risk factor for peripheral arterial disease and stroke [56, 57]. Thus, all men with ED should be screened for CAD, with evaluation for related comorbidities where appropriate. In fact, the Princeton III consensus guidelines, an expert opinion report, recognize ED as a strong predictor of CVD and CAD and recommend screening of men presenting with ED for CVD risk factors [58]. A recent economic analysis found that screening of men with ED for CVD

risk factors and treating these at-risk men can result in an approximately tenfold cost savings when compared with treatment of ED and CVD-related sequelae [59].

The association between ED and CVD is predicated on the similarities between the pathophysiologies of the two conditions. Penile erection depends on healthy vascular endothelium and the release of NO and other factors that promote corporal smooth muscle relaxation, an increase in arterial inflow, and a decrease in venous outflow. Disruptions in normal endothelial function can impair penile blood flow. Similarly, the pathophysiology of CVD is related to endothelial cell dysfunction, resulting in decreased NO release and predisposing to atherosclerosis and decreased blood flow. Other mechanisms that may contribute to endothelial dysfunction include increased peripheral sympathetic activity, alterations in vascular structure that limit vascular dilation and blood flow, and higher levels of inflammatory mediators [26, 27, 32, 60, 61]. ED may be the first sign of CVD, in part due to the differences in caliber between penile and coronary arteries. Penile arteries are 1–2 mm in diameter, in contrast with the left anterior descending coronary artery, which is 3–4 mm. Thus, an atherosclerotic plaque of equal size in either vessel will more likely compromise flow in the penile artery, leading to ED symptoms prior to CAD symptoms [62].

Diabetes and ED

Diabetes mellitus is a common risk factor for ED, with ED present in 35–90 % of diabetic men [63] and occurring three times more frequently in diabetics than nondiabetics (49.3 % vs. 15.6 %, respectively) [64]. Both Type 1 and Type 2 diabetics are at increased risk of developing ED, with a relative risk (RR) of 3.0 for Type 1 and RR of 1.3 for Type 2 diabetics when compared with nondiabetic men (Table 5.3) [65]. The risk of ED in Type 2 diabetics increases with duration of diabetes, with an RR of 1.7 in men having diabetes for more than 20 years [65, 66].

While no published trials comparing the impact of glycemic control on ED are available, several studies support good glycemic control leading to improvement in ED symptoms. Glycosylated hemoglobin (hemoglobin A1c) is strongly associated with ED (OR 3.70) and provides a good long-term indicator of glycemic control [67]. In the Diabetes Control and Complications Trial, 761 Type 1 diabetic men were randomized to either intensive or conventional glycemic control. The study evaluated two cohorts: a primary prevention cohort, consisting of 366 men with diabetes of 1–5-year duration and without evidence of microvascular complications, and the secondary intervention cohort, consisting of 395 men with diabetes of 1–15-year duration and evidence of nonproliferative retinopathy and/or microalbuminuria. An ancillary study to the trial evaluated ED in 571 men (295

Table 5.3 Risk factors and risk of developing ED

ED risk factor	Relative risk (RR) or odds ratio (OR) (95 % confidence interval)
Diabetes mellitus (DM) [65]	
Type 1 DM	RR 3.0 (1.5–5.9)
Type 2 DM <20-year duration	RR 1.3 (1.1–1.5)
Type 2 DM >20-year duration	RR 1.7 (1.1–2.7)
Hemoglobin A1c (Hgb A1c) [67]	
Hgb A1c >5.7–6.4 %	OR 1.7 (1.1–2.8)
Hgb A1c ≥6.5 %	OR 3.7 (2.2–6.3)
Smoking [75]	
Current smokers	OR 1.5 (1.3–1.7)
Former smokers	OR 1.3 (1.1–1.5)
Obesity (overall) [82]	RR 1.9 (1.6–2.2)
Body Mass Index (BMI) (kg/m^2) [82]	
BMI 25.0–26.9	RR 1.2 (1.1–1.3)
BMI 27.0–29.9	RR 1.3 (1.1–1.4)
BMI ≥30	RR 1.7 (1.5–2.0)
Physical activity [85]	
Low physical activity	OR 1.0 (reference)
Moderate physical activity	OR 0.6 (0.4–0.9)
High physical activity	OR 0.4 (0.2–0.8)

from the primary prevention and 280 from the secondary intervention cohorts) and found a lower ED rate in the intensive glycemic control group compared to the conventional glycemic control group for the secondary intervention cohort (12.8 % vs. 30.8 %) [68]. Importantly, the risk of developing ED was associated with baseline mean hemoglobin A1c (HbA1c), with every 10 % increase in mean HbA1c resulting in a 55 % increased odds of ED symptoms in the secondary cohort and 21.5 % in the primary cohort.

The pathophysiology of ED in diabetes is likely multifactorial. Glycemic dysregulation contributes to macrovascular atherosclerotic disease via endothelial dysfunction and other mechanisms and also leads to microvascular complications, resulting in nerve ischemia and subsequent damage, which manifests as autonomic and peripheral neuropathy. Penile innervation via the dorsal and perineal nerves includes sympathetic and parasympathetic fibers, as well as motor and sensory somatic nerves. ED can result from impaired parasympathetic stimulation resulting from autonomic neuropathy that impedes corporal cavernosal smooth muscle relaxation [63]. Diabetic peripheral neuropathy can also predispose to venous leak by impairing sensory impulse transmission from the penile shaft and glans to the reflexogenic erectile center, as well as transmission of motor impulses to the bulbocavernosus and ischiocavernosus muscles responsible for preventing venous outflow from the cavernous bodies [43]. Diabetes is often associated with concurrent hypogonadism, with 20 % of diabetic men having hypogonadal serum testosterone levels and 31 % of diabetic men having borderline low testosterone levels [69].

Hypertension and ED

Hypertension is a risk factor for CVD and contributes to systemic endothelial dysfunction, thus linking it to ED. In the National Health and Nutrition Examination Survey (NHANES) of 2126 American men, the age-adjusted prevalence of ED was 27.7 % in men with treated hypertension and 15.1 % in men with untreated hypertension [14]. The higher prevalence of ED in men with treated hypertension underscores the contribution of antihypertensive medications in the development of ED. Many antihypertensives, including diuretics, nonselective beta-blockers, and alpha-2 blockers, can cause ED, while angiotensin-converting enzyme inhibitors and calcium channel blockers typically do not have adverse effect on erectile function. Other studies have also demonstrated an association between hypertension and ED. The Massachusetts Male Aging Study (MMAS), a cross-sectional survey of over 1700 men aged 40–69 from Massachusetts, found a direct association between hypertension and ED [13]. In contrast, a cross-sectional observational study of 1242 hypertensive men evaluating the impact of treating hypertension on ED found that 6 months or more of treatment using beta-blockade resulted in a lower ED prevalence independent of age, CVD, or medical treatment [70]. Another study evaluating 1007 patients also found that antihypertensive therapy using nebivolol, the same beta-blocker found to be effective in the prior study, resulted in a lower prevalence of ED [71]. The beneficial effects of nebivolol may be related to the drug's unique ability to act as a vasodilator by potentiating NO release. Thus, while antihypertensive medications can be causal in the development of ED, hypertension alone, as a CVD risk factor, can increase the risk of ED in affected men.

ED and Smoking

A relationship between ED and smoking has been identified and is likely linked to the negative effects of smoking on the vasculature that result in increased cardiovascular complications in smokers. While incompletely understood, the etiology of smoking's deleterious effects on erectile function likely results from endothelial dysfunction. Smoking causes increased levels of reactive oxygen species (ROS) that can negatively affect endothelial cells, leading to increased oxidative stress and decreased bioavailability of the NO required for smooth muscle relaxation in the corpora cavernosa [72].

Several clinical and epidemiological studies have demonstrated a clear association between ED and smoking. After adjusting for age and other covariates, data from the MMAS showed that cigarette smokers had a higher risk of moderate or severe ED (24 % vs. 14 %) when compared to nonsmokers [73], a finding supported by a cross-sectional survey of 4462 Vietnam War veterans, which also found an increased risk of ED (adjusted OR 1.5) in smokers [74]. A recent meta-analysis of eight studies encompassing 28,856 patients found an odds ratio (OR) of 1.51 in current smokers and 1.29 in former smokers with ED, further supporting an increased risk of ED in smokers [75]. A prospective clinical trial evaluating the impact of smoking cessation on ED found an improvement in ED symptoms in 25 % of men who stopped smoking when compared with men who continued smoking [76]. Importantly, a significant correlation between the severity of ED and amount of smoking was also observed, further suggesting that a direct impact of smoking on the vasculature may contribute to the development of ED in these men. A more recent study compared penile tumescence, assessed using plethysmography, in men who stopped smoking during an 8-week smoking cessation program with those who relapsed [77]. In men who successfully quit smoking, improvements in both penile tumescence response and in the time it took to reach maximum sexual arousal were observed.

Obesity and Sedentary Lifestyle in Men with ED

Obesity and sedentary lifestyle are also significant risk factors for ED. Even in the absence of other ED risk factors, the presence of obesity can increase the risk of ED. In two large, cross-sectional population studies, elevated body mass index (BMI) was a predictor of ED [78, 79]. Other studies have identified obesity, a lack of exercise, insulin resistance, and the metabolic syndrome as independent risk factors for ED [73, 80]. The MMAS observed a higher incidence of ED in obese men with sedentary lifestyles [81]. In a multivariate analysis as part of the Health Professionals Follow-Up Study, a cohort study of 22,086 American men 40–75 years old, obesity increased the risk of ED as a function of BMI [82]. Compared to men with normal BMI (<25 kg/m^2), those with BMI 25–26.9 kg/m^2 had a 19 % increased risk of developing ED, while those with a BMI 27–29.9 kg/m^2 had a 33 % increased risk of developing ED.

Perhaps more importantly, treatment of obesity and increased activity can improve ED symptoms. A randomized, single-blind trial of 110 men with a mean BMI of 36 kg/m^2 and mean IIEF score 13.7 evaluated the effects of weight loss on ED. The intervention group was advised on how to lose at least 10 % of their body weight through physical activity and reduced caloric intake, whereas the control group was only given general information about healthy food choices and exercise. After 2 years, the intervention group had a significant decrease in BMI and a statistically significant increase in IIEF scores when compared with controls [83]. Multivariate analysis revealed that changes in body mass and physical activity were independently associated with changes in IIEF scores. More recently, a prospective cohort study evaluated the effects of physical activity on ED in hypertensive men with ED aged 50–70 years [84]. An experimental group of 22 hypertensive men with ED was assigned an 8-week exercise program and compared to age-matched controls, and significant improvements in IIEF scores were observed in the exercise group when compared with controls. These findings are supported by at least one other prospective study, which also demonstrated an inverse relationship between physical activity and ED [82]. A meta-analysis evaluating seven cross-sectional studies identified a negative correlation between physical activity and ED (OR 0.53) as well as a dose-response relationship between physical activity and ED, with OR = 1 for low activity, OR = 0.63 for moderate activity, and OR = 0.42 for high activity [85].

Similar to other cardiovascular risk factors, the impact of obesity on ED is likely related to the detrimental effects of inflammation on endo-

thelial function. Chronic inflammation can result from excessive calorie intake and physical inactivity, which may lead to overproduction of pro-inflammatory cytokines including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [86]. Upregulation of these cytokines leads to low-grade inflammation that impairs endothelial function, primarily by decreasing NO bioavailability, which can also predispose to atherosclerosis [87]. Clinically, men with ED have higher serum CRP levels when compared with age- and comorbidity-matched controls [88], which are lower in men with ED after exercise, coinciding with improvement in IIEF scores [84]. Elevated CRP levels have also been associated with greater severity of penile arterial disease as measured using penile Doppler ultrasound in men with ED [89].

ED and Lower Urinary Tract Symptoms

Benign prostatic hypertrophy (BPH) and lower urinary tract symptoms (LUTS) have also been linked to ED, and the pathophysiologies of BPH/LUTS and ED may be related [90]. Men with LUTS manifest a higher prevalence of ED, which increases with LUTS severity [1, 91, 92]. Bladder neck obstruction in animal models results in increased cavernosal smooth muscle tone and worse erectile function [93, 94]. Importantly, PDE5 is highly expressed in genital tissues, and PDE5is decrease genital muscle contraction in a dose-dependent manner [95]. Clinical studies have shown improvement in IIEF and International Prostate Symptom Scores (IPSS) in men treated with PDE5is, with a significant improvement in urinary flow in men taking sildenafil [96, 97]. A recent meta-analysis evaluating PDE5i and alpha-blocker therapy, alone or in combination, in men with ED and LUTS associated with BPH encompassing 515 men demonstrated significant improvements in IIEF, IPSS, and maximal urinary flow values in men on combination therapy when compared with PDE5i therapy alone [98].

Hypogonadism and ED

A link between hypogonadism and ED has been forged in recent years, with approximately 12 % of men with ED having coincident hypogonadism [99]. The third Princeton Consensus Conference recommends the use of testosterone therapy in men with ED who are also hypogonadal [58]. Testosterone therapy may ameliorate both ED symptoms as well as cardiovascular risk, with a meta-analysis showing overall improvement in 57 % of men with ED [100], with improvements in ED symptoms in 39 % [39], and improvements in sexual performance, desire, and motivation as well [40]. To further support a link between testosterone and erectile function, serum testosterone levels correlate with onset of sexual symptoms, with decrements in libido at serum levels of 430 ng/dL and onset of ED symptoms at serum testosterone levels of 230–300 ng/dL [101]. However, it is important to counsel patients starting on testosterone therapy that symptomatic improvement may only become evident after 4–12 weeks of therapy. In addition, approximately 30 % of men with ED treated with PDE5is alone do not respond [102], whereas concomitant administration of testosterone with PDE5is in hypogonadal men results in greater improvement in erectile function when compared with men receiving placebo and PDE5i [17].

To further support a role for hypogonadism and hormonal alterations in male sexual function, several studies have explored the role of human chorionic gonadotropin (hCG) and clomiphene citrate on sexual function in hypogonadal men. Both hCG and Clomid can raise serum testosterone levels via direct and indirect testicular stimulation, respectively. Unlike the use of exogenous testosterone, which can result in infertility by suppressing sperm production, stimulation of testicular testosterone production is beneficial in hypogonadal men with ED who wish to achieve fatherhood. The use of hCG to raise testosterone levels increases sexual activity in 50 % of men with normal testosterone levels [103]. Similarly, when clomiphene citrate was used to normalize testosterone levels, improvement in sexual function was observed in 39 % of treated men [104].

Hypogonadism and ED are often linked to obesity. While the precise mechanism of obesity-related hypogonadism is unknown, it is likely linked to hormonal alterations given the essential contribution of testosterone to normal erectile function and the high incidence of hypogonadism and ED in obese men [39, 105]. Testosterone is involved in many aspects of male sexual arousal and function, and suppression of testosterone in men may result in ED and sexual dysfunction [106–108]. In animal models, androgens are essential in the regulation of nitric oxide synthase (NOS), PDE5 activity, and penile muscle cells, supporting the clinical finding that PDE5i efficacy is increased after correction of hypogonadism [17, 109].

ED and Depression

Much work has focused on organic risk factors for ED, but ED is also linked to psychological parameters. While psychogenic ED can result from anxiety and the resultant adrenergic stimulation, depressive symptoms also play a significant role in the predisposition to ED. The MMAS found an increased risk of ED in men with depressive symptoms (OR 1.82) [110]. In a study of 2173 men in the Male Attitudes Regarding Sexual Health Study, men with depressive symptoms had a higher likelihood of LUTS (OR 2.68) and ED (OR 1.73) than men without depressive symptoms [111]. The study also identified a racial proclivity for depressive symptoms, observing that Hispanic and black men with ED were significantly more likely to report depressive symptoms than white men. Other studies have also identified a relationship between ED and depression [112]. When considering psychogenic ED, the link with sexual confidence and performance anxiety should not be overlooked. Numerous studies have identified a link between ED and sexual confidence or performance anxiety [113, 114], relationship concerns, loss of self-esteem [113], and other psychosocial stresses [21], all of which should be considered in men presenting with ED.

The Role of Lifestyle Modification in Mitigating the Risk of ED

The third Princeton Consensus Conference recommends lifestyle adjustment in men with ED to not only reduce cardiovascular risk but also improve ED symptoms [58]. Recommended lifestyle alterations include smoking cessation, regular exercise, dietary intervention with emphasis on the Mediterranean diet, and moderate alcohol consumption. The incorporation of lifestyle modifications to decrease or reverse the impact of ED and cardiovascular risk factors is described above for many individual risk factors. More generally, however, several other studies support the use of lifestyle modification for symptomatic improvement in ED. A 2011 meta-analysis encompassing 740 participants demonstrated improvements in the Sexual Health in Men (SHIM) scores after ≥6 weeks of lifestyle alteration [115]. While lifestyle modifications benefit ED symptoms, these changes are most beneficial for primary prevention, with smoking cessation reducing cardiovascular mortality by 36% [116], physical activity reducing the risk of DM and CAD by 30–50% [117], and diet reducing CAD-related death by 36% [118].

Conclusions

ED is the most common male sexual dysfunction, with a rising prevalence in part due to an aging population, but also due to increased incidence in obesity and other associated risk factors. ED can significantly limit the quality of life of affected men and can be a harbinger of systemic conditions, namely, cardiovascular disease, which can significantly impact morbidity and mortality in affected men. The etiology of ED is complex and often multifactorial, involving one or more organic factors, as well as psychogenic contributors in most cases; few men have completely isolated organic ED, whereas isolated psychogenic ED may occur in a minority of men. The risk factors for developing ED are numerous, with age at the top of the list, but also including factors that parallel the etiologic underpinnings of ED. Diabetes

mellitus, cardiovascular disease, and risk factors that predispose to these conditions, including obesity, smoking, and hypertension, detrimentally impact the vasculature and can result in ED as an initial or early presentation of the above conditions, particularly cardiovascular disease. Many of the risk factors and etiologies for ED are inextricably intertwined, and the commonalities between the pathogenic mechanisms that result in vascular compromise are important to keep in mind.

Address of ED risk factors using lifestyle modification, together with medical and surgical therapy where appropriate, can mitigate the impact of ED. Given the relationship between ED and its associated comorbidities, the role of specialty physicians treating men with ED is expanded to include screening for comorbid conditions that can shorten life with appropriate referral to appropriate treating physicians. Continued investigation of the molecular mechanisms of ED and the growing list of related conditions, which often distill down to a common pathogenic mechanism, will continue to expand our understanding of ED and possible targets for intervention.

References

1. Braun M, et al. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. Int J Impot Res. 2000;12(6):305–11.
2. Lindau ST, et al. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762–74.
3. NIH Consensus Conference. Impotence. NIH consensus development panel on impotence. JAMA. 1993;270(1):83–90.
4. Mykletun A, et al. Assessment of male sexual function by the Brief Sexual Function Inventory. BJU Int. 2006;97(2):316–23.
5. O'Leary MP, et al. Distribution of the Brief Male Sexual Inventory in community men. Int J Impot Res. 2003;15(3):185–91.
6. Panser LA, et al. Sexual function of men ages 40 to 79 years: the Olmsted County Study of Urinary Symptoms and Health Status Among Men. J Am Geriatr Soc. 1995;43(10):1107–11.
7. Muller MJ, et al. Quality of partnership in patients with erectile dysfunction after sildenafil treatment. Pharmacopsychiatry. 2001;34(3):91–5.
8. Litwin MS, Nied RJ, Dhanani N. Health-related quality of life in men with erectile dysfunction. J Gen Intern Med. 1998;13(3):159–66.
9. Shabsigh R, et al. Increased incidence of depressive symptoms in men with erectile dysfunction. Urology. 1998;52(5):848–52.
10. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int. 1999;84(1):50–6.
11. Lue TF. Erectile dysfunction. N Engl J Med. 2000;342(24):1802–13.
12. Lewis RW, et al. Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med. 2010;7(4 Pt 2):1598–607.
13. Feldman HA, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151(1):54–61.
14. Selvin E, Burnett SL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med. 2007;120(2):151–7.
15. Laumann EO, et al. Prevalence and correlates of erectile dysfunction by race and ethnicity among men aged 40 or older in the United States: from the male attitudes regarding sexual health survey. J Sex Med. 2007;4(1):57–65.
16. Tsertsvadze A, et al. Diagnosis and treatment of erectile dysfunction. Evidence reports/technology assessments, vol. 171. Rockville, MD: Agency for Healthcare Research and Quality (US); 2009.
17. Shabsigh R, et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. J Urol. 2004;172(2):658–63.
18. Lin CS, Lin G, Lue TF. Cyclic nucleotide signaling in cavernous smooth muscle. J Sex Med. 2005;2(4):478–91.
19. Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381(9861):153–65.
20. Jin L, Burnett AL. RhoA/Rho-kinase in erectile tissue: mechanisms of disease and therapeutic insights. Clin Sci (Lond). 2006;110(2):153–65.
21. Rosen RC. Psychogenic erectile dysfunction. Classification and management. Urol Clin North Am. 2001;28(2):269–78.
22. Lizza EF, Rosen RC. Definition and classification of erectile dysfunction: report of the Nomenclature Committee of the International Society of Impotence Research. Int J Impot Res. 1999;11(3):141–3.
23. Deveci S, et al. Can the International Index of Erectile Function distinguish between organic and psychogenic erectile function? BJU Int. 2008;102(3):354–6.
24. Siddiqui MA, et al. Erectile dysfunction in young surgically treated patients with lumbar spine disease: a prospective follow-up study. Spine (Phila PA 1976). 2012;37(9):797–801.

25. Saenz de Tejada I, et al. Pathophysiology of erectile dysfunction. J Sex Med. 2005;2(1):26–39.
26. Jackson G. The importance of risk factor reduction in erectile dysfunction. Curr Urol Rep. 2007; 8(6):463–6.
27. Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. Lancet. 1985;1(8422):181–4.
28. Sullivan ME, et al. Nitric oxide and penile erection: is erectile dysfunction another manifestation of vascular disease? Cardiovasc Res. 1999;43(3):658–65.
29. Chew KK, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. J Sex Med. 2010;7(1 Pt 1):192–202.
30. Giuliano FA, et al. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. Urology. 2004;64(6):1196–201.
31. Martin-Morales A, et al. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. J Urol. 2001;166(2):569–74. discussion 574-5.
32. Corona G, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol. 2011;165(5):687–701.
33. Mulhall JP. Penile rehabilitation following radical prostatectomy. Curr Opin Urol. 2008;18(6):613–20.
34. Traish AM, et al. Effects of castration and androgen replacement on erectile function in a rabbit model. Endocrinology. 1999;140(4):1861–8.
35. Traish AM, et al. Adipocyte accumulation in penile corpus cavernosum of the orchidectomized rabbit: a potential mechanism for veno-occlusive dysfunction in androgen deficiency. J Androl. 2005;26(2): 242–8.
36. Morgentaler A, Feibus A, Baum N. Testosterone and cardiovascular disease – the controversy and the facts. Postgrad Med. 2015;127(2):159–65.
37. Rhoden EL, et al. The relationship of serum testosterone to erectile function in normal aging men. J Urol. 2002;167(4):1745–8.
38. Corona G, et al. Aging and pathogenesis of erectile dysfunction. Int J Impot Res. 2004;16(5):395–402.
39. Isidori AM, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. Eur Urol. 2014;65(1):99–112.
40. Wang C, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab. 2000;85(8):2839–53.
41. Corona G, et al. Effect of hyperprolactinemia in male patients consulting for sexual dysfunction. J Sex Med. 2007;4(5):1485–93.
42. Aversa A, et al. Early endothelial dysfunction as a marker of vasculogenic erectile dysfunction in young habitual cannabis users. Int J Impot Res. 2008;20(6):566–73.
43. Thomas A, et al. Urologic complications of nonurologic medications. Urol Clin North Am. 2003;30(1): 123–31.
44. Baumhakel M, et al. Cardiovascular risk, drugs and erectile function—a systematic analysis. Int J Clin Pract. 2011;65(3):289–98.
45. Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. Int Clin Psychopharmacol. 2011;26(3):130–40.
46. El-Sakka AI. Association of risk factors and medical comorbidities with male sexual dysfunctions. J Sex Med. 2007;4(6):1691–700.
47. Montorsi F, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol. 2003;44(3):360–4. discussion 364-5.
48. Jackson G, et al. Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. Int J Clin Pract. 2010;64(7):848–57.
49. Montorsi P, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J. 2006;27(22):2632–9.
50. Vlachopoulos C, et al. Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. Eur Urol. 2005;48(6):996–1002. discussion 1002-3.
51. Inman BA, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc. 2009;84(2):108–13.
52. Vlachopoulos CV, et al. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes. 2013;6(1): 99–109.
53. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol. 2011;58(13):1378–85.
54. Guo W, et al. Erectile dysfunction and risk of clinical cardiovascular events: a meta-analysis of seven cohort studies. J Sex Med. 2010;7(8):2805–16.
55. Thompson IM, et al. Erectile dysfunction and subsequent cardiovascular disease. JAMA. 2005;294(23): 2996–3002.
56. Polonsky TS, et al. The association between erectile dysfunction and peripheral arterial disease as determined by screening ankle-brachial index testing. Atherosclerosis. 2009;207(2):440–4.
57. Ponholzer A, et al. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? Eur Urol. 2005;48(3):512–8. discussion 517-8.
58. Nehra A, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87(8):766–78.

59. Pastuszak AW, et al. Erectile dysfunction as a marker for cardiovascular disease diagnosis and intervention: a cost analysis. J Sex Med. 2015;12(4): 975–84.
60. Mittawae B, et al. Incidence of erectile dysfunction in 800 hypertensive patients: a multicenter Egyptian national study. Urology. 2006;67(3):575–8.
61. Burchardt M, et al. Hypertension is associated with severe erectile dysfunction. J Urol. 2000;164(4): 1188–91.
62. Montorsi P, Montorsi F, Schulman CC. Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? Eur Urol. 2003;44(3):352–4.
63. Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. J Sex Med. 2009;6(5):1232–47.
64. Ponholzer A, et al. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. Eur Urol. 2005;47(1):80–5. discussion 85-6.
65. Bacon CG, et al. Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. Diabetes Care. 2002;25(8):1458–63.
66. Kalter-Leibovici O, et al. Clinical, socioeconomic, and lifestyle parameters associated with erectile dysfunction among diabetic men. Diabetes Care. 2005;28(7):1739–44.
67. Weinberg AE, et al. Diabetes severity, metabolic syndrome, and the risk of erectile dysfunction. J Sex Med. 2013;10(12):3102–9.
68. Wessells H, et al. Effect of intensive glycemic therapy on erectile function in men with type 1 diabetes. J Urol. 2011;185(5):1828–34.
69. Kapoor D, et al. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care. 2007;30(4):911–7.
70. Cordero A, et al. Erectile dysfunction may improve by blood pressure control in patients with high-risk hypertension. Postgrad Med. 2010;122(6): 51–6.
71. Cordero A, et al. Erectile dysfunction in high-risk hypertensive patients treated with beta-blockade agents. Cardiovasc Ther. 2010;28(1):15–22.
72. Tostes RC, et al. Cigarette smoking and erectile dysfunction: focus on NO bioavailability and ROS generation. J Sex Med. 2008;5(6):1284–95.
73. Feldman HA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med. 2000; 30(4):328–38.
74. Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? Am J Epidemiol. 1994;140(11):1003–8.
75. Cao S, et al. Smoking and risk of erectile dysfunction: systematic review of observational studies with meta-analysis. PLoS One. 2013;8(4), e60443.
76. Pourmand G, et al. Do cigarette smokers with erectile dysfunction benefit from stopping? A prospective study. BJU Int. 2004;94(9):1310–3.
77. Harte CB, Meston CM. Association between smoking cessation and sexual health in men. BJU Int. 2012;109(6):888–96.
78. Blanker MH, et al. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. J Am Geriatr Soc. 2001;49(4):436–42.
79. Bacon CG, et al. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med. 2003;139(3): 161–8.
80. Esposito K, Giugliano D. Obesity, the metabolic syndrome, and sexual dysfunction. Int J Impot Res. 2005;17(5):391–8.
81. Derby CA, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology. 2000;56(2):302–6.
82. Bacon CG, et al. A prospective study of risk factors for erectile dysfunction. J Urol. 2006;176(1): 217–21.
83. Esposito K, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 2004;291(24):2978–84.
84. Lamina S, Okoye CG, Dagogo TT. Therapeutic effect of an interval exercise training program in the management of erectile dysfunction in hypertensive patients. J Clin Hypertens (Greenwich). 2009;11(3):125–9.
85. Cheng JY, et al. Physical activity and erectile dysfunction: meta-analysis of population-based studies. Int J Impot Res. 2007;19(3):245–52.
86. Vlachopoulos C, et al. Inflammation, metabolic syndrome, erectile dysfunction, and coronary artery disease: common links. Eur Urol. 2007;52(6): 1590–600.
87. Trepels T, Zeiher AM, Fichtlscherer S. The endothelium and inflammation. Endothelium. 2006;13(6):423–9.
88. Yao F, et al. Subclinical endothelial dysfunction and low-grade inflammation play roles in the development of erectile dysfunction in young men with low risk of coronary heart disease. Int J Androl. 2012; 35(5):653–9.
89. Billups KL, et al. Relation of C-reactive protein and other cardiovascular risk factors to penile vascular disease in men with erectile dysfunction. Int J Impot Res. 2003;15(4):231–6.
90. Glina S, Glina FP. Pathogenic mechanisms linking benign prostatic hyperplasia, lower urinary tract symptoms and erectile dysfunction. Ther Adv Urol. 2013;5(4):211–8.
91. Nicolosi A, et al. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology. 2003;61(1):201–6.
92. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537–44.
93. Chang S, et al. Increased corpus cavernosum smooth muscle tone associated with partial bladder outlet

obstruction is mediated via Rho-kinase. Am J Physiol Regul Integr Comp Physiol. 2005;289(4):R1124–30.
94. Kobayashi K, et al. Animal model for the study of the relationship between lower urinary tract symptoms/bladder outlet obstruction and erectile dysfunction. Int J Urol. 2011;18(10):710–5.
95. Tinel H, et al. Pre-clinical evidence for the use of phosphodiesterase-5 inhibitors for treating benign prostatic hyperplasia and lower urinary tract symptoms. BJU Int. 2006;98(6):1259–63.
96. Gacci M, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol. 2012;61(5):994–1003.
97. Ozturk MI, et al. Acute effects of sildenafil on uroflowmetric parameters in erectile dysfunction patients with and without lower urinary tract symptoms. J Androl. 2012;33(6):1165–8.
98. Yan H, et al. The efficacy of PDE5 inhibitors alone or in combination with alpha-blockers for the treatment of erectile dysfunction and lower urinary tract symptoms due to benign prostatic hyperplasia: a systematic review and meta-analysis. J Sex Med. 2014;11(6):1539–45.
99. Gore J, Rajfer J. The role of serum testosterone testing: routine hormone analysis is an essential part of the initial screening of men with erectile dysfunction. Rev Urol. 2004;6(4):207–10.
100. Jain P, Rademaker AW, McVary KT. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. J Urol. 2000;164(2):371–5.
101. Porst H, et al. SOP conservative (medical and mechanical) treatment of erectile dysfunction. J Sex Med. 2013;10(1):130–71.
102. Tsertsvadze A, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. Ann Intern Med. 2009;151(9):650–61.
103. Buvat J, Lemaire A, Buvat-Herbaut M. Human chorionic gonadotropin treatment of nonorganic erectile failure and lack of sexual desire: a double-blind study. Urology. 1987;30(3):216–9.
104. Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. J Clin Endocrinol Metab. 1995;80(12):3546–52.
105. Chughtai B, et al. Metabolic syndrome and sexual dysfunction. Curr Opin Urol. 2011;21(6):514–8.
106. Shabsigh R. Testosterone therapy in erectile dysfunction and hypogonadism. J Sex Med. 2005;2(6):785–92.
107. Blute M, et al. Erectile dysfunction and testosterone deficiency. Front Horm Res. 2009;37:108–22.
108. Buvat J, et al. Endocrine aspects of male sexual dysfunctions. J Sex Med. 2010;7(4 Pt 2):1627–56.
109. Shabsigh R, et al. The evolving role of testosterone in the treatment of erectile dysfunction. Int J Clin Pract. 2006;60(9):1087–92.
110. Araujo AB, et al. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med. 1998;60(4):458–65.
111. Laumann EO, et al. Lower urinary tract symptoms are associated with depressive symptoms in white, black and Hispanic men in the United States. J Urol. 2008;180(1):233–40.
112. Perelman MA. Erectile dysfunction and depression: screening and treatment. Urol Clin North Am. 2011;38(2):125–39.
113. Althof SE, Wieder M. Psychotherapy for erectile dysfunction: now more relevant than ever. Endocrine. 2004;23(2-3):131–4.
114. Morse WI, Morse JM. Erectile impotence precipitated by organic factors and perpetuated by performance anxiety. Can Med Assoc J. 1982;127(7):599–601.
115. Gupta BP, et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011;171(20):1797–803.
116. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA. 2003;290(1):86–97.
117. Bassuk SS, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J Appl Physiol (1985). 2005;99(3):1193–204.
118. Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. Circulation. 2008;117(23):3031–8.

Making the Diagnosis of Erectile Dysfunction

6

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Introduction

Erectile dysfunction is defined as the consistent inability to both attain and maintain an erection of the penis sufficient to permit satisfactory sexual intercourse. The original NIH definition in 1992 did not define a specific interval of symptoms; however, subsequent definitions include a 3-month minimum duration, not including unique trauma-related or postsurgical cases [1, 2]. Both physician and patient factors impact the low screening and consultation rate of ED in relation to its high prevalence. Factors from the physician perspective include busy clinic schedules, perceived insignificance of ED in relation to other urologic conditions, and bias toward patient age. From a patient perspective, embarrassment is the most common barrier; however, lack of sexual interest or acceptance of the condition is another potential obstacle to seeking treatment [3].

It is important for physicians to be not only receptive to those patients presenting with ED, but to specifically ask if patients have concerns regarding their sexual function. From the epidemiologic point of view, ED can be related to several major diseases, including hypertension, cardiovascular disease, dyslipidemia, diabetes, and depression [4]. Though ED is not commonly thought of as a presenting symptom of these prevalent conditions, the concept of screening for ED in these high-risk populations should be encouraged.

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Diagnosis of ED: Basic Diagnostic Tools

Sexual History

The first step in diagnosing ED is confirming it, as patients frequently confuse ED with other sexual dysfunctions including premature ejaculation and inability to reach orgasm. Privacy and confidentiality are essential when addressing ED, as well as the demonstration of trust and empathy in order to allow the patient to feel comfortable discussing sensitive, personal, and

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traditionally taboo issues. Assumptions should never be made about sexual orientation or number of partners, and the practitioner should use clear, simple, and straightforward language in order to help the patient feel at ease. With the patient's approval, the partner can also be involved in the interview process in order to expand on aspects of the history and identify goals of treatment. Circumstances surrounding specific partners and overall relationship health should be elucidated to help identify precipitating factors. Other key questions include type of stimuli used during sexual encounters, the presence of nocturnal erections, and the ability to self-stimulate. As with other medical problems, it is important to establish the onset of the symptom (duration), as well as severity (mild, moderate, severe) and timing (once, always, situational) to help confirm the dysfunction and identify the diagnosis.

Questionnaires

Questionnaires can be helpful and simple tools used to assess the presence or severity of ED, especially in those settings where the interviewer is not familiar with the condition and when a measurable clinical response is needed. Although questionnaires are a subjective tool with information from the patient's interpretation and self-response, they can serve as objective data to assess treatment response or disease progression. One of the most widely used questionnaires is the International Index of Erectile Function (IIEF) [5], a 15-item questionnaire covering five domains including desire, erection, orgasm, ejaculation, and satisfaction, with scores ranging from 1 to 5 per question. A lengthy questionnaire at 15 questions with 1–5 ratings each is often used in clinical trials, but may be a tedious task for consultation. An abbreviated version of this questionnaire is the IIEF erectile function domain, comprised of five questions focused on the erection domain and sexual satisfaction with a maximum score of 30. Men with a normal erectile function will have a score of ≥25. It is important to note that a "0" score is possible if the patient has not attempted intercourse. This may make interpretation of results challenging, but further discussion with the patient can clarify true erectile function.

A simplified questionnaire derived from the IIEF is the Sexual Health Inventory for Men (SHIM) and includes five questions on erectile function during the prior 6 months. Here, a total score ranges from 5 to 25 (Fig. 6.1): a score of 22–25 conveys normal erectile function, 17–21 mild ED, 12–16 mild to moderate ED, 8–11 moderate ED, and <7 severe ED [6].

Medical History

The primary goal of the medical history is to identify possible underlying causes and risk factors for ED. The association between ED and multiple medical conditions is well demonstrated [4], and a detailed history may uncover specific reversible causes of ED (smoking, alcoholism, obesity, lack of exercise, medications) or treatable factors (vascular disease, diabetes mellitus, hypertension, depression/anxiety, hyperlipidemia). Other conditions such as spinal cord injury, neurologic dysfunction, history of pelvic radiation, and history of trauma are also highly associated with ED. These often dictate specialized management and are important to elicit in the history. Additionally, a focused urologic history should be obtained, specifically asking about history of genital trauma, Peyronie's disease, priapism, and GU cancers. Identification of any prior abdominal or GU surgeries is also important, especially prostatectomy and pelvic or spinal surgery that have the potential to disrupt nerve pathways. Finally, a thorough review of the patient's current medications is mandatory to rule out possible contributors to ED and avoid potential treatment contraindications.

History taking should follow a template that allows the interviewer to identify the different risks and predisposing factors, with the intention to act on each of them with a clear therapeutic purpose (Fig. 6.2). Ultimately, the goal of the

Over the past 6 months:

1. How do you rate your confidence that you could get and keep an erection?

2. When you had erections with sexual stimulation, howoften were your erections hard enough for penetration?

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

5. When you attempted sexual intercourse, how often was it satisfactory for you?

Fig. 6.1 Sexual Health Inventory for Men (SHIM) questions

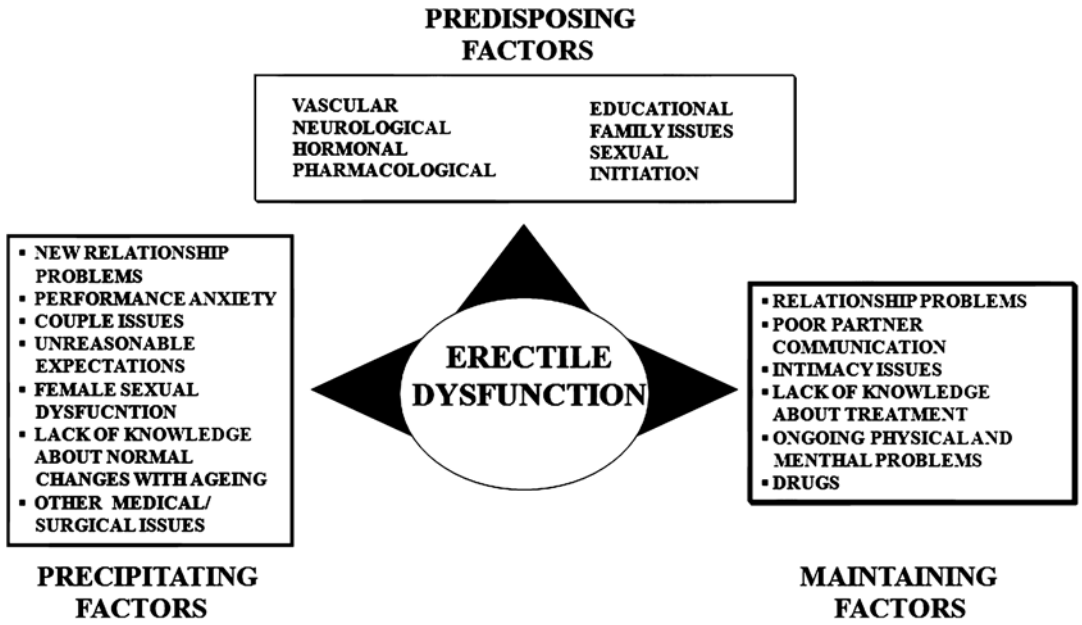

Fig. 6.2 Risk factors for erectile dysfunction. (Used with permission from Hackett G, Kell P, Ralph D, Dean J, Price D, Speakman M et al. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. The Journal of Sexual Medicine 2008; 5:1841–1865)

history is to differentiate between organic and psychogenic ED, with the classic differentiation being the presence of waking erections in psychogenic cases. However, patients cannot always be cleanly dichotomized into one category, and ED often falls along a spectrum from physiologic to psychological [7]. Additionally, ED may initially be organic in nature, but develop into psychogenic ED as a man loses confidence and develops performance anxiety.

Sexual Function and Aging

Another important aspect of the interview is the patient and partner's degree of knowledge regarding normal changes in sexual function with aging, including anticipated decrease in testosterone levels. This decrease may be secondary to a decline in Leydig cells, a reduction of LH peaks, impaired tissue perfusion, and/or an increase of the serum sex hormone-binding globulin [8, 9].

The concept that ED is a normal part of aging is a common myth. It is important to explain to both patient and partner that though sexual response may change with aging, including longer time for arousal and orgasm and increased refractory period, erectile dysfunction is not a sequela of aging alone [8]. However, the Massachusetts Male Aging Study showed a clear relationship of ED with age and reported a prevalence of ED as high as 52 % in men over 40 years of age [10]. This is likely secondary to an increase in prevalence in common diseases that lead to ED, such as cardiovascular disease and diabetes. An adrenergic over-sensibility or hyperactivity and a decrease of penile smooth muscle may also contribute to decreased function. Also, it is important to remember that everyone ages differently, and "average" sexual function will differ for each individual man.

These changes need to be discussed with patients as they often result in a lower sexual frequency, a longer time needed to achieve a rigid erection, a need for a greater stimulus to obtain a similar response, lower penetration rigidity, lower ejaculatory volume, and faster detumescence. It is also valuable to discuss the normal physiologic changes that occur in the female partner, such as the physical and psychological changes that occur during menopause and female sexual dysfunction.

Physical Examination

A focused physical examination is mandatory in assessing the patient complaining of ED. Though unlikely to reveal an exact etiology, the exam may reveal underlying risk factors. Height, weight, BMI, and vital signs should always be obtained. The presence of hypertension, weak or absent femoral and distal pulses, and obesity may suggest a vascular causation. A thorough genital exam should be performed, observing for penile plaques, foreskin retraction, prepubic fat, testis size, and presence of masses or cysts. A brief neurologic exam should also be performed to identify any alterations in sensation that may inhibit arousal or suggest an underlying neurologic disorder. Appearance of body habitus and degree of secondary sex characteristics can be important in identifying an underlying endocrine etiology. Any discomfort or pain with exam should also be noted. Finally, a rectal exam is important to assess rectal tone and reflexes, as well as for routine evaluation of prostate cancer in men over 50 [11].

Laboratory Tests

As discussed previously, many medical conditions can contribute to ED, and it is important to obtain labs that may uncover previously undiagnosed conditions. A panel including basic chemistries, complete blood count, fasting glucose, lipid profile, and serum total testosterone makes up the initial lab evaluation for most patients presenting with ED. The total testosterone should be sent from a morning blood draw and if low should trigger further investigation with free testosterone and luteinizing hormone. This helps to delineate the location of the deficiency along the hypothalamic-pituitary-gonadal axis (Fig. 6.3). Thyroid hormones may also be considered in patients with symptoms of either hypo- or hyperthyroidism. Further specialized laboratory testing can be determined on a case-by-case basis.

Establishing Cardiovascular Risk

It is not uncommon to uncover risk factors previously unknown to the patient, most frequently diabetes, dyslipidemia, or hypertension [12, 13].

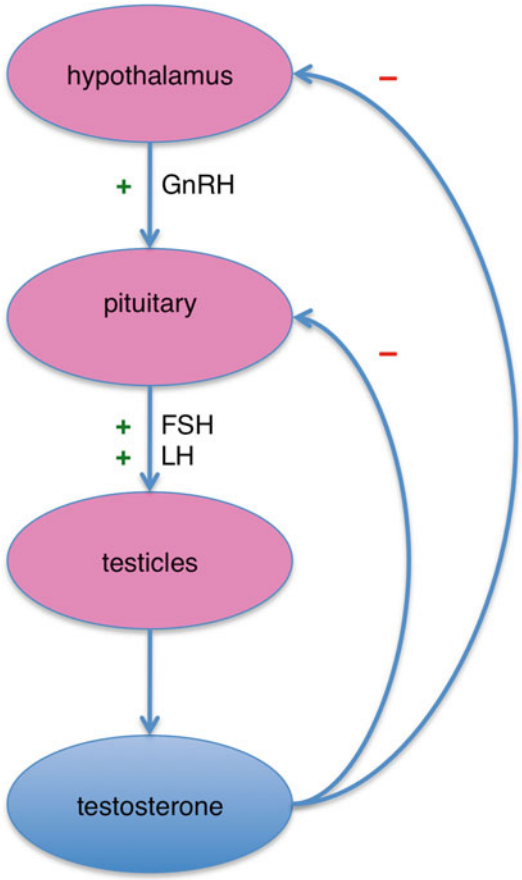

Fig. 6.3 The hypothalamic-pituitary-gonadal axis

General risk factors for cardiovascular disease include increased age, male sex, family history, smoking, hypertension, hypercholesterolemia, diabetes, obesity, and physical inactivity. In 1999, a panel of experts expanded on the guidelines for cardiovascular evaluation in patients with ED [14] and established three levels of cardiovascular risk with corresponding management recommendations [15].

Low-Risk Category

Asymptomatic; <3 risk factors for coronary artery disease ([CAD] excluding gender); uncomplicated past myocardial infarction (MI); left ventricular dysfunction (LVD)/congestive heart failure (CHF) (New York Heart Association [NYHA] class I); mild, stable angina (evaluated and/or being treated); post-successful coronary revascularization; controlled hypertension; and mild valvular disease. The management of low-risk patients is as follows: primary care management, consider all first-line therapies, and reassess at regular intervals (6–12 months).

Intermediate-Risk Category

>3 risk factors for CAD (excluding gender); recent MI (>2, <6 weeks); moderate, stable angina; LVD/CHF (NYHA class II); and noncardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease). The management of intermediate-risk patients is as follows: specialized CV testing (e.g., exercise treadmill test [ETT], Echo) and re-stratification into high risk or low risk based on the results of CV assessment.

High-Risk Category

High-risk arrhythmias; unstable or refractory angina; recent MI (<2 weeks); LVD/CHF (NYHA class III/IV); uncontrolled hypertension; moderate-to-severe valvular disease; hypertrophic obstructive; and other cardiomyopathies. The management of high-risk patients is as follows: priority referral for specialized CV management and treatment for sexual dysfunction to be deferred until cardiac condition is stabilized and dependent on specialist recommendations.

First Consultation for ED: What Are Our Goals?

An integrated approach that includes a sexual and medical history, physical exam, and basic laboratory testing will help the clinician narrow focus on the primary etiology of a man's ED along the spectrum of organic to psychogenic causation. Other medical conditions that may be underlying contributors are commonly identified, including diabetes, dyslipidemia, hypertension, cardiovascular disease, and depression. The initial consultation may also be the first opportunity to educate the patient and partner on the expected changes of sexual function in the

aging male. It also provides a unique opportunity to counsel lifestyle changes as an effective fulcrum for behavior change. In many cases, improved sexual function may be a greater motivator for smoking cessation than the intangible decrease in cardiac risk. This approach facilitates efficient treatment of ED and can potentially detect previously undiagnosed serious medical problems.

Additional Diagnostic Tools

In most cases, the treatment plan for ED can be devised without invasive or specialized diagnostic testing. However, some unique cases will require extensive investigation, and this section reviews those tests performed to further delineate between the vasculogenic, neurogenic, endocrine, and psychogenic causes of ED. The broader appreciation of the physiology and pathophysiology of erectile function, variable specificity and sensitivity of specialized diagnostic tests, the availability of effective oral treatment, and the efforts to evaluate and treat patients while maximizing patient comfort and quality of life have minimized the importance of precisely identifying the exact cause of ED. As such, a more goal-oriented approach to diagnosing ED is currently used, without the use of historical testing and invasive diagnostic studies [16, 17].

A thorough evaluation for a specific cause of ED is limited to certain situations in which a confirmed diagnosis or modified therapeutic treatment plan is needed. In general, candidates needing a more specific evaluation are:

1. Nonresponders to oral medication
2. Post-traumatic ED
3. Candidates for penile implant
4. Peyronie's disease
5. Post-priapism ED
6. Lifelong (primary) ED
7. Medicolegal situations
8. At patient request

Nocturnal Penile Tumescence and Rigidity Test

Nocturnal and morning erections are physiologic events occurring during rapid eye movement (REM) sleep. Nocturnal erections provide oxygenation of the penile tissues, an event necessary to preserve function and tissue tropism. A normal man will have between four and six erections during sleep. Evaluation of nocturnal erections has been performed since the early 1970s [18]. This evaluation can be done in conjunction with a full sleep lab (rarely indicated) or as a stand-alone ambulatory test using the RigiScan® (GOTOP Medical, St. Paul, MN) device (Fig. 6.4a–d). The RigiScan assessment should take place over the course of two nights, with the goal of an erectile event of at least 60 % rigidity recorded on the tip of the penis lasting for 10 min or more; this outcome is considered indicative of a functional erectile mechanism [19]. In theory, a man who has normal erectile episodes during sleep and complains of ED could potentially be experiencing psychogenic ED; therefore the confirmation of nocturnal erections typically distinguishes organic from psychogenic ED [11]. Though the RigiScan device is both a sensitive and specific testing method, inquiring about the presence and strength of nocturnal erections is a more cost effective and minimally invasive strategy. Though outdated, the "stamp test" was historically used as a simple technique to evaluate presence of nocturnal erections. This involved wrapping a roll of four to six stamps around the flaccid penis and noting if the roll of stamps was broken in the morning. Performed for three straight nights, a consistent morning disruption of stamps likely indicated the presence of normal nocturnal erections.

Pharmacological Erection Test

The pharmacological erection test involves the intracavernosal injection of vasoactive agents. The test should be performed with the patient in

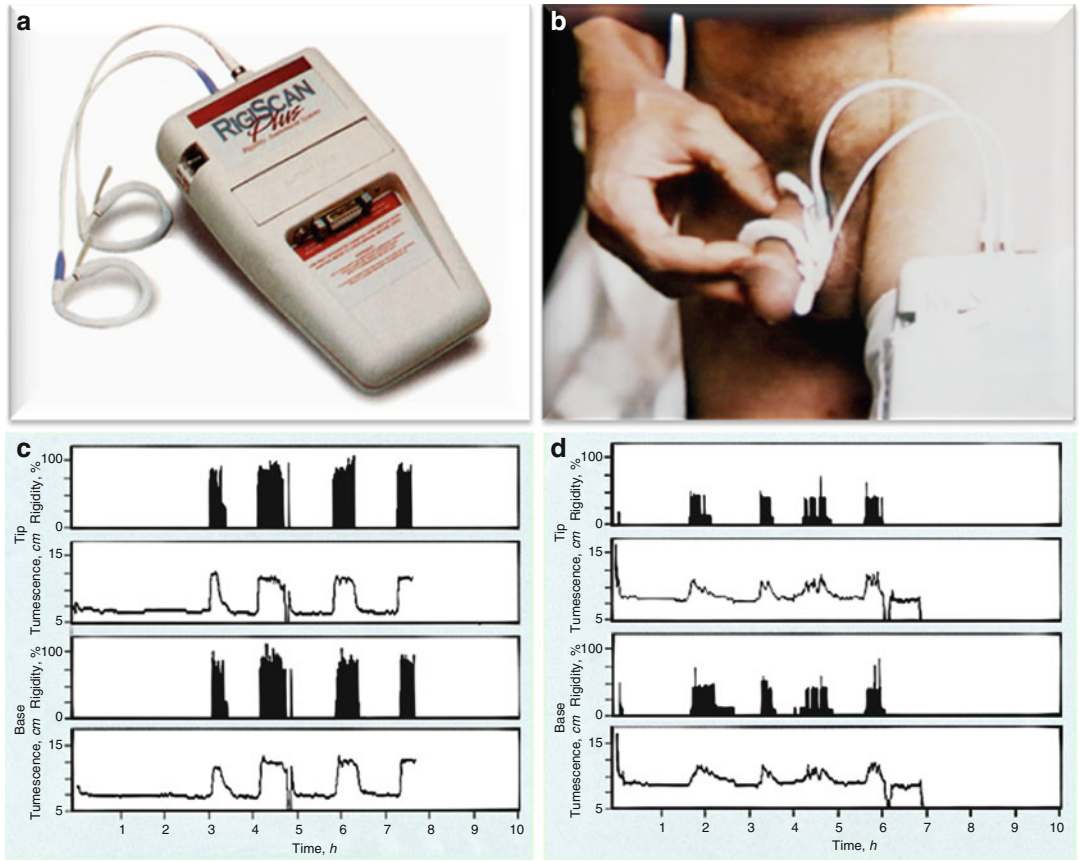

Fig. 6.4 **a**–**d**) The RigiScan® test: (**a**) RigiScan® patient unit. (Used with permission of GOTOP Medical, Inc, St. Paul, MN.) (**b**) Device on the patient. (**c**) Normal tracing. (**d**) Abnormal tracing

a comfortable, private room, with or without visual and/or self-stimulation. It is a practical and simple office-based diagnostic tool, with normal response resulting in an erection lasting 30 min and rigid enough for penetration (Fig. 6.5a, b).

Although it does not provide a direct vascular evaluation, it is useful in the following settings:

- Indirect evaluation of the corporo-occlusive mechanism. A normal response (rigid erection) may still be obtained in the presence of arterial insufficiency; however, a normal response demonstrates the integrity of veno-occlusive function [20–22].
- Evaluation of penile curvatures either congenital or due to Peyronie's disease. It allows the clinician to assess the degree of the curvature and plan a surgical correction if necessary.
- Evaluation of the erectile response and demonstration of a self-injection program. The titration phase will help determine the right dose and drug choice.

The most widely used drugs for intracavernosal injections are papaverine, phentolamine, and alprostadil (semisynthetic prostaglandin E1); the latter is the most commonly used as a single drug, but mixtures of papaverine and phentolamine, or the three drugs together (known as *trimix*), are being used globally [23, 24]. There is no consensus on the standard drug or dose to use, although 20 μg of alprostadil or 0.25 mL of trimix is most

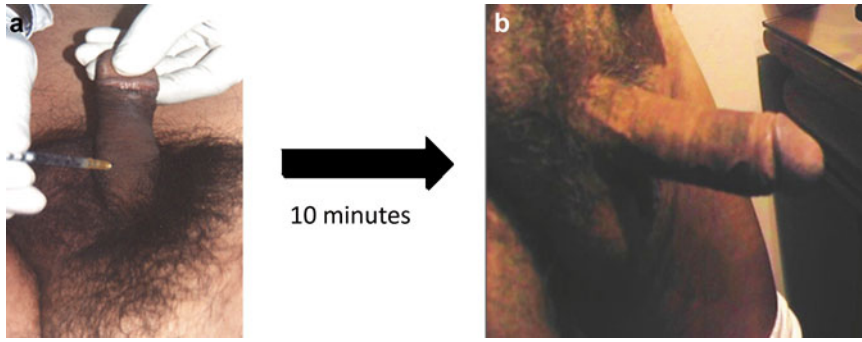

Fig. 6.5 (**a**, **b**) Pharmacological erection test. (**a**) Vasoactive drugs are injected intracavernosally. (**b**) Full response at 10 min postinjection

frequently used [25]. It is extremely important to counsel patients on the need to seek medical care for erections lasting longer than 4 h. These cases may require injection of phenylephrine into one side of the corpora cavernosum. Classically, phenylephrine is diluted with normal saline to create a final concentration of 100–500 μg/mL, and 1 mL is administered every 3–5 min until detumescence is achieved [26].

Duplex/Doppler Penile Ultrasound

This test involves the hemodynamic evaluation of the cavernous arteries and penile structures through a color duplex/Doppler (DDPU) ultrasound using a high-frequency linear probe (7.5–10 MHz). This gives the investigator insight into the arterial blood supply of the penis, the veno-occlusive mechanism, corporal and tunica fibrosis or plaques, and an evaluation of penile deformities. The examination is performed after an intracavernosal injection of a vasoactive drug as a pharmacologic erection test and followed by self-stimulation and/or re-dosing with multiple injections until an erection similar to the best at-home erection is achieved. Of note, a prospective study examining repeat Doppler ultrasounds demonstrated that nearly 50 % of patients were misdiagnosed with a venous leak and actually had entirely normal hemodynamics. These false-positive errors can be decreased by performing adequate re-dosing to achieve optimal erections, in turn improving the accuracy of Doppler penile ultrasound [27].

Common indications for duplex/Doppler penile ultrasound (DDPU) include:

- Patients nonresponsive to oral or intracavernosal vasoactive agents
- Patients considered candidates for revascularization surgery
- Priapism
- Peyronie's disease patients considered candidates for reconstructive surgery
- Patient request for in-depth investigation

The original technique was introduced by Lue and Hricak in 1985 [28], and the following parameters are evaluated during DDPU at 5 and 20 min postinjection of the vasoactive agent [29–31] (Fig. 6.6a, b):

- Peak systolic velocity – normal values: ≥30 cm/s
- End-diastolic velocity – normal values: ≤5 cm/s
- Resistance index – normal values: ≥0.85–0.9

Dynamic Infusion Cavernosometry and Cavernosography

This test was widely used up until the late 1990s when a goal-directed approach was adopted and PDE5 inhibitors became available. However, its indication is now restricted to specific situations

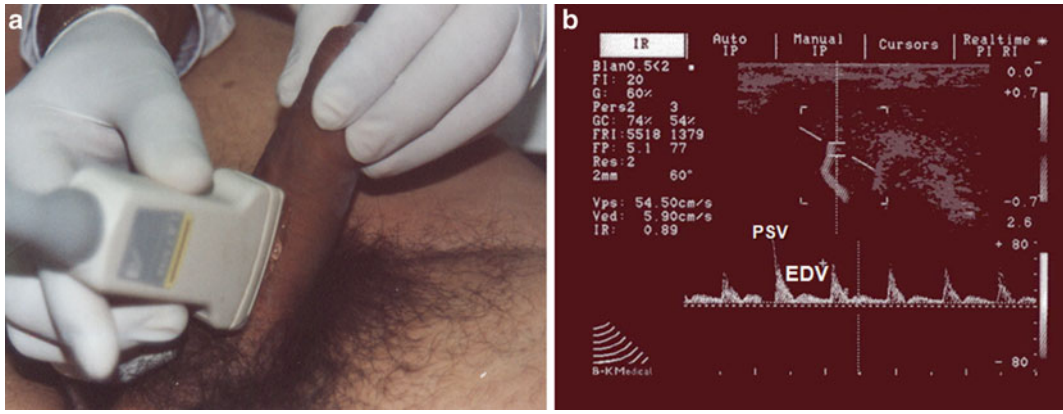

Fig. 6.6 (**a**, **b**) Duplex/Doppler penile ultrasound. (**a**) High-frequency probe on the dorsal aspect of the penis. (**b**) Cavernosal artery tracing showing peak systolic velocity (PSV) and end-diastolic velocity (EDV)

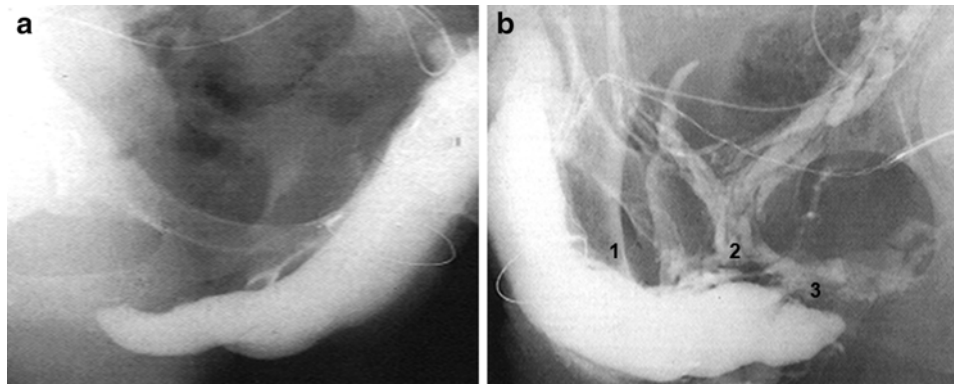

Fig. 6.7 (**a**, **b**) Dynamic cavernosography. (**a**) Normal, no venous leak. (**b**) Abnormal venous leak. *1* dorsal vein, *2* cavernosal veins, *3* crural veins

where revascularization or, more rarely, venous surgery is considered.

This is a dynamic test performed under high doses of intracavernosal vasoactive agents to maximize smooth muscle relaxation. This minimally invasive test involves the insertion of two intracavernosal butterfly needles (one for pump infusion and one for pressure monitoring), with three phases recorded:

- *Phase* 1: recording of intracavernosal pressure curve after injection
- *Phase* 2: recording of the cavernosal pressure decay curve from 150 mmHg in 30 s and/or flow to maintain a rigid erection with a pressure of 90–100 mmHg
- *Phase* 3: evaluation of the arterial Doppler signal when exposed to a suprasystolic intracavernosal pressure [11, 29, 32]

The last phase of the study is the cavernosography, which is performed under fluoroscopic monitoring using nonionic contrast that fills both corpora and assesses the venous drainage systems (dorsal, cavernosal, and crural veins). Radiographs are then obtained in anterior/posterior and oblique/lateral projections (Fig. 6.7a, b).

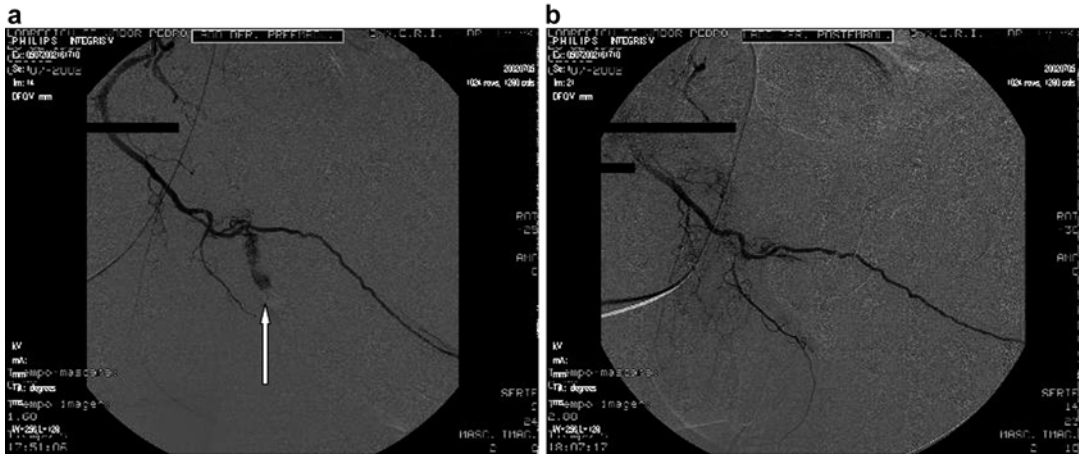

Fig. 6.8 (**a**, **b**) Penile angiography. (**a**) Patient with a high-flow priapism, *arrow* shows cavernous artery fistula. (**b**) Post-fistula embolization

Phalloarteriography

The use of DDPU has replaced penile angiography as the standard vascular evaluation in men with ED. This technique was widely used in the early 1980s, but is now only indicated in young men with suspicion of a single vascular lesion in the absence of general vascular risk factors and those men with a high-flow priapism. These patients may be considered candidates for a revascularization or embolization procedure, respectively [11, 17, 33] (Figs. 6.7a, b and 6.8a, b).

Summary: Working Toward a Diagnostic Algorithm

It the ideal world, the management of ED would be standardized into a simple algorithm for diagnosis and treatment. However, each patient presents with a different and unique set of situations and expectations. Below, we summarize the basic approach to diagnosing ED and present an algorithm to provide a framework for workup and treatment.

The first step is to compose a focused history and identify the chief complaint, as frequently the patient may confuse ED with other disorders of sexual dysfunction. Once the presence of ED is established, the interviewer should appreciate how, when, where, and with whom he has dysfunction. The patient and partner's expectations should also be explored, as sexual function changes in both men and women with aging. Most importantly, privacy and sensitivity are of the utmost importance, allowing the patient to express his concerns in a confidential fashion while providing basic education on sexual function.

Physical examination will include basic urologic (genitalia and rectal exam), vascular (blood pressure and peripheral pulses), endocrine (secondary sexual characteristics, fat and hair distribution), and neurological assessment (bulbocavernosus reflex and genital sensation). Routine laboratory tests are ordered with the intention of detecting diabetes, dyslipidemia, or kidney function or evaluating for an endocrinopathy. Prostate cancer screening is discussed and offered when indicated.

The algorithm below presents a structure for integrating the evaluation of ED and identifies unique situations where further specialized and diagnostic tests may be warranted (Fig. 6.9).

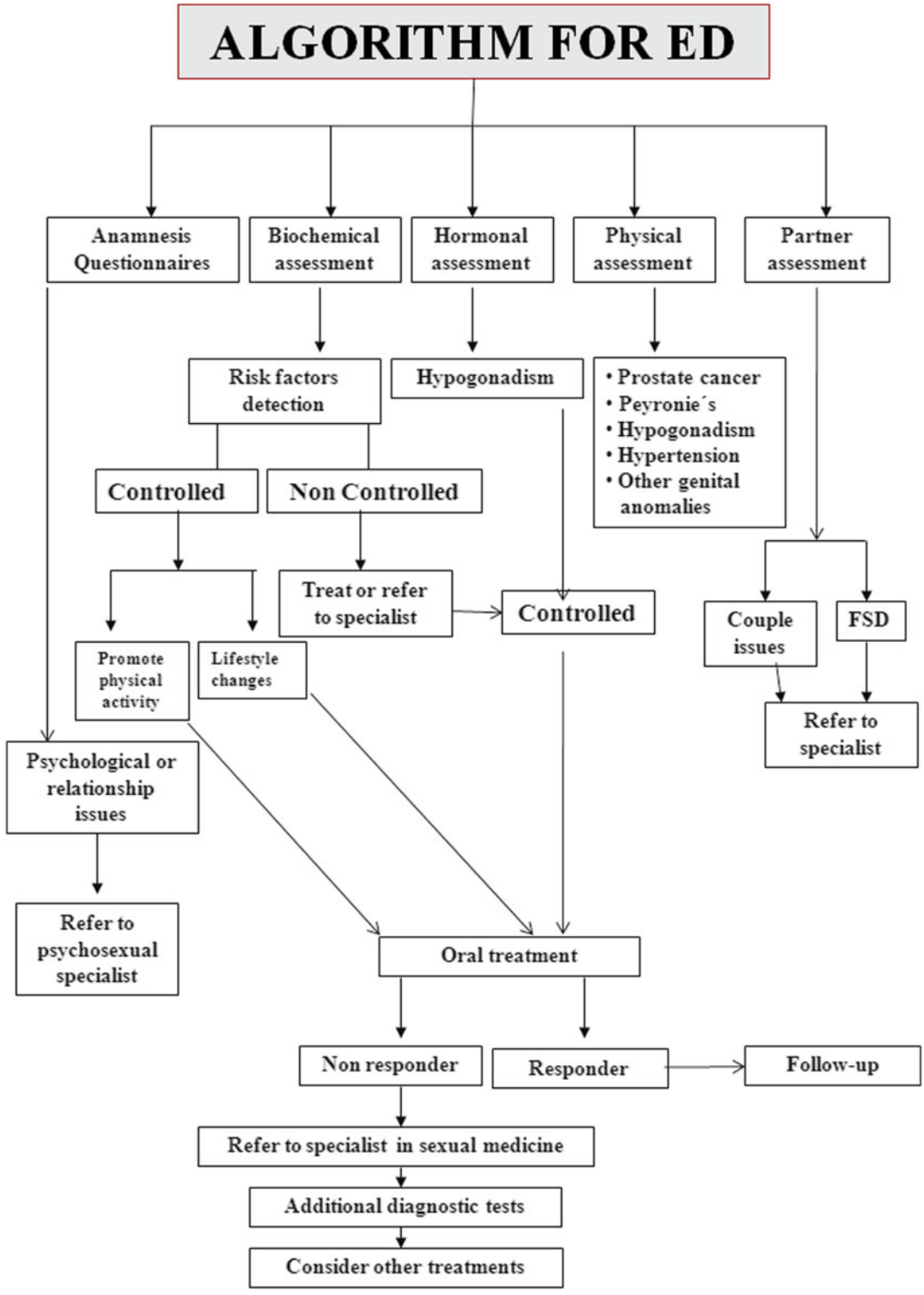

Fig. 6.9 Proposed diagnostic algorithm for ED

References

1. NIH Consensus Statement: Impotence. 1992;10: 1–33.
2. Lewis RW, Fugl-Meyer KS, Bosch R, et al. Epidemiology/risk factors of sexual dysfunction. J Sex Med. 2004;1:35–9.
3. Rosen RC, Hatzichristou D, Broderick G, et al. Clinical evaluation and assessment in men. In: Lue TF, Basson R, Rosen R, editors. Sexual medicine: sexual dysfunctions in men and women. Paris: Health Publications; 2004. p. 173–220.
4. Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J Urol. 2004;171:2341–5.
5. 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(6):822–30.
6. Cappelleri JC, Rosen RC. The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. Int J Impot Res. 2005;17(4):307–19.
7. Ralph D, McNicholas T. UK management guidelines for erectile dysfunction. BMJ. 2000;321:499–503.
8. Morales A, Lunenfeld B. Investigation, treatment and monitoring of late-onset hypogonadism in males. Aging Male. 2002;5:74–86.
9. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999;84:3666–72.
10. 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.
11. Seftel AD. Diagnosis of erectile dysfunction. In: Porst H, Buvat J, editors. Standard practice in sexual medicine. Oxford: Blackwell Publishing; 2006. p. 59–74.
12. 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:S60–4.
13. 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;12:305–11.
14. DeBusk R, Drory Y, Goldstein I, Jackson G, Kaul S, Kimmel SE, et al. Management of sexual dysfunction in patients with cardiovascular disease: Recommendations of The Princeton Consensus Panel Sexual. Am J Cardiol. 2000;86:175–81.
15. Rosen G, Kloner RC, Kostis RA. The second Princeton consensus on sexual dysfunction and cardiac risk: new guidelines for sexual medicine. J Sex Med. 2006;3:28–36.
16. 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 Sex Med. 2004;1:49–57.
17. Hackett G, Kell P, Ralph D, Dean J, Price D, Speakman M, et al. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. J Sex Med. 2008;5:1841–65.
18. Karacan J, Salis PJ, Thornby JI, et al. The ontogeny of nocturnal penile tumescence. Walk Sleep. 1976;1: 27–44.
19. 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;159:1921–6.
20. 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;36:60–7.
21. Pescatori E, Hatzchiristou D, Namburi S, Goldstein I. A positive intracavernous injection test implies normal veno-occlusive but not necessarily normal arterial function: a haemodynamic study. J Urol. 1994;151: 1209–16.
22. Cormio L, Nisen H, Selvaggi F, Ruutu M. A positive pharmacological erection does not rule out arteriogenic erectile dysfunction. J Urol. 1996;156:1209–16.
23. Bechara A, Casabé A, Cheliz G, et al. Prostaglandin E1 versus mixture of prostaglandin El, papaverine and phentolamine in non-responders to high papaverine plus phentolamine doses. J Urol. 1996;155:913–4.
24. Bechara A, Casabé A, Chéliz G, et al. Comparative study of papaverine plus phentolamine versus prostaglandin E1 in erectile dysfunction. J Urol. 1997; 157:2132–4.
25. Bennett AH, Carpenter AJ, Barada JH. An improved drug combination for a pharmacologic erection program. J Urol. 1991;146:1564–5.
26. Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, Nehra A, Sharlip ID. Members of the erectile dysfunction guideline update panel, American Urological Association. J Urol. 2003;170(4 Pt 1):1318.
27. Teloken PE, Park K, Parker M, et al. The false diagnosis of venous leak: prevalence and predictors. J Sex Med. 2011;8:2344–9.
28. Lue T, Hricak H, Marich K, et al. Vasculogenic impotence evaluated by high-resolution ultrasonography and pulsed Doppler spectrum analysis. Radiology. 1985;155:777.
29. Sanchez-Ortiz R, Broderick G. Vascular evaluation of erectile dysfunction. In: Mulchay J, editor. Male sexual function: a guide to clinical management. Totowa, NJ: Humana Press Inc; 2011. p. 167–202.
30. Meuleman EJ, Diemont WL. Investigation of erectile dysfunction. Diagnostic testing for vascular factors in

erectile dysfunction. Urol Clin North Am. 1995; 22:803–19.
31. Momesso A, Beche E. Duplex Doppler penile ultrasound. Curr Sex Health Rep. 2006;3:107–9.
32. Sharlip I, Jarow J, Rajfer J. Post Graduate Course: H0252 Pm. Diagnosis and treatment of erectile dysfunction. 96th annual meeting. American Urological Association, Inc.; 2002.
33. Ciampalini S, Savoca G, Buttazzi L, Gattuccio I, Mucelli FP, Bertolotto M, et al. High-flow priapism: treatment and long-term follow-up. Urology. 2002;59:110–3.

Hormonal Evaluation and Therapy of Erectile Dysfunction

7

Mark S. Hockenberry and Puneet Masson

Introduction

Significant controversy currently exists regarding the evaluation of hypogonadism and its treatment. The controversy, in part, is heightened by dramatic recent increases in testosterone (T) replacement therapy (TRT) prescriptions. In the USA between 2001 and 2011, TRT prescriptions increased more than threefold from 0.81 to 2.91 % in men over 40 years old [1]. Over that same time period, TRT pharmaceutical sales worldwide increased 12-fold alongside heavy marketing of new transdermal applications with resultant global costs increasing from $150 million to $1.8 billion [2].

Research supports widespread misuse and overuse of TRT. Of concern, about 25 % men received a TRT prescription without a T level assessed in the 12 months prior [1]. An analysis of insurance claims data revealed that over 60 % of men received a TRT prescription directly from their primary care doctors without evaluation by either endocrinologists or urologists [3]. TRT misuse extends even to urologists as evidenced by a survey of American Urological Association (AUA) members with 25 % of respondents incorrectly employing TRT to treat a young infertile man attempting pregnancy [4]. Additionally, the overuse of TRT encompasses the treatment of erectile dysfunction (ED) in eugonadal men. In 2013, the first inaugural publication of the "Choosing Wisely" program compiled the five most overused tests or procedures submitted by each medical specialty and included the following admonishment on the list offered by the AUA: Do not prescribe T to men with ED who have normal T levels [5].

Recent evidence suggesting a possible association between TRT and increased cardiovascular risk, coupled with the exploding costs and misuse of TRT, has elevated the controversy to a fever pitch that lay media attention has extended to the general public. In January 2014, the US Food and Drug Administration (FDA) announced an investigation into the risks of stroke, heart attack, and death in men on TRT following studies that documented increased risk [6–8]. As covered in The New York Times, an FDA expert panel voted in September 2014 to impose stricter regulations for packaging language regarding TRT indications and to require clinical trials assessing TRT safety

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[9]. However, the statistical validity of these studies documenting increased risk has been extensively questioned [10]. Furthermore, a large body of literature supports a possible protective effect of TRT with regard to reducing one's risk of obesity [11], insulin resistance [12], heart attacks [13], and overall mortality [14]. The true relationship between T and cardiovascular risk remains to be fully elucidated.

A complex interplay exists between hypogonadism, cardiovascular risk factors, and ED. ED is associated with many cardiovascular risk factors, such as aging, the metabolic syndrome, and smoking, and consequently serves as an important marker of decreased cardiovascular health. ED precedes coronary artery disease in one half of patients [15]. Men presenting with ED have a 1.48 relative risk of cardiovascular event occurring within 2–5 years of ED onset [16]. Hypogonadism is associated with similar cardiovascular risk factors as with ED [17]. Indeed, sexual dysfunction is the most specific symptom of late-onset hypogonadism and about one third of men presenting with sexual dysfunction are hypogonadal [18].

Evidence suggests that T influences the physiology of erections in several ways through its effects on the nervous system as well as penile vasculature and tissues [19]. TRT clearly improves libido but research supporting its role for improving ED is less clear [20]. Despite the controversy and limitations in the literature, there is a role for hormonal evaluation in patients with sexual dysfunction and hormone replacement in selected patients with hypogonadism. This chapter will discuss the nuances in diagnosis and management of hormone abnormalities in ED with a focus on T and brief description of other hormone imbalances.

Prevalence of Hypogonadism

The actual prevalence of hypogonadism in the population is difficult to assess due to several factors including a lack of consensus regarding its definition. The intraday variability of T and sporadic application of age-reference standards to adjust for T declines with aging constitute further methodological challenges. The Hypogonadism in Males study found that 39 % of men over 45 years old presenting to a primary care doctor were hypogonadal based on laboratory assessment [21]. Approximately 6 % of middle-aged to older men were found to experience symptomatic hypogonadism in a population-based survey [22].

Prevalence of Hypogonadism Among Patients with Sexual Dysfunction

The prevalence of both hypogonadism and sexual dysfunction increases with age and with comorbid conditions, such as coronary artery disease and obesity [22, 23]. Although the European Male Aging Study demonstrated a correlation between hypogonadism and sexual dysfunction including decreased libido and erections [18], insufficient literature exists to clearly show a higher prevalence of hypogonadism in ED patients relative to age-matched controls [24]. Estimates of the prevalence of hypogonadism among patients presenting with ED range from 7 to 47 % varying with T level cutoffs from less than 200 ng/dl to less than 400 ng/dl [25]. Pooled data from over 7000 ED patients revealed that 4 % of men less than 50 years old were hypogonadal compared to about 15 % of men over 50 years old [20]. A rigorous trial including serial T testing found only a 6.6 % prevalence of hypogonadism among ED patients [26].

Definition of Hypogonadism

No precise, universally agreed upon definition of hypogonadism exists. In general, the term hypogonadism refers to insufficient testicular function both to produce a normal quantity of sperm and physiologic amounts of T. In the context of this chapter, hypogonadism will refer specifically to androgen deficiency. Hypogonadism may result from primary testicular failure, secondary testicular failure due to low gonadotropin and abnormalities of the hypothalamic–pituitary–gonadal

axis, a combination of both primary and secondary testicular failure, or androgen receptor mutations. T also declines naturally with age and decreases about 1–2 % per year [27].

Hypogonadism represents a clinical syndrome and should only be diagnosed in men with consistent signs and symptoms of androgen deficiency in addition to unequivocally low serum T levels [28]. Features suggestive of hypogonadism may be nonspecific. According to the Endocrine Society guidelines, more specific features include delayed sexual development, reduced libido, decreased spontaneous erections, delayed orgasm, breast discomfort or enlargement, loss of body hair, small or shrinking testes, low bone mineral density, or hot flashes. Less specific features include decreased energy or motivation, depressed mood, poor concentration, irritability, sleep disturbance, reduced muscle mass, increased body fat, or diminished physical performance [28]. Validated questionnaires, such as the Androgen Deficiency of the Aging Male questionnaire, may assist in the assessment of these signs and symptoms but all suffer from low specificity because these features may be easily influenced by age or other comorbidities [29]. Table 7.1 displays the Androgen Deficiency of the Aging Male questionnaire as adapted from Morley et al. [30]. The typical range of circulating total T in middle-aged men is between 300 and 1000 ng/dl for most laboratory tests [31]. Although symptom onset and severity varies according to the individual, most symptoms present below a threshold of approximately 300 ng/dl [32]. An initial evaluation of a man with suspected hypogonadism should begin with a detailed history and physical examination to assess for these symptoms and signs before proceeding to a laboratory evaluation. Testosterone screening in asymptomatic men is not currently indicated.

Table 7.1 Androgen deficiency in the aging male screening questionnaire

Question
1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decrease in "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Adapted with permission from Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49:1239–42

A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any three other questions

Laboratory Evaluation of Hypogonadism

The laboratory evaluation of hypogonadism can be complex and defies standardization and universal agreement. In addition to existing in several forms, T levels also fluctuate with time and other processes. Normal T ranges vary between individuals. Furthermore, T is difficult to measure; several assays are currently utilized and each has its own inherent variability.

Several different types of T exist in serum due to its lipophilic nature and poor solubility in water. Consequently, most T is bound to circulating proteins with about 60 % of total T tightly bound to sex hormone binding globulin and about 38 % loosely bound to albumin. About 2 % of total T is unbound and called free T. Bioavailable T refers to the T available to interact with androgen receptors and constitutes free T as well as most T bound to albumin [20].

Theoretically, low levels of free or bioavailable T should correspond to clinical hypogonadism whereas total T may be less relevant. Equilibrium dialysis is the gold standard assay for determination of free T, but this method is rarely used and only possible in specialized laboratories. Other methods to assess free T are also technically challenging with questionable accuracy and include a direct assay measuring a T analogue and quantification of sex hormone binding globulin by precipitation with ammonium.

The current most widely accepted method of measuring free T relies on calculating the level from a formula based on total T and sex hormone binding globulin [33]. This calculated free T is not routinely computed by laboratories and, given the difficulties of assessing free and bioavailable T, most practitioners rely on total T levels. Commercially available assays for total T are relatively cheap and have been demonstrated by mass spectrometry to be reliable [34].

Several vagaries also impede the precise determination of total T levels, however. Assay outcomes are often specific to reagents and execution of the tests within given laboratories. Therefore, laboratories must develop individual reference ranges. Additionally, debate continues regarding the appropriate reference range for a given patient as to whether the reference should be a range for a typical young man or a range adjusted for age based on the natural decrease of T with time [35]. T also demonstrates a diurnal circadian rhythm of secretion with higher levels in the morning and thus obtaining blood in the afternoon may lead to a false appearance of abnormally low levels, though this circadian effect is blunted in older patients. Indeed, about 29 % of men with ED and an initial low total T were found to have normal T levels on subsequent testing [36].

Several conditions may alter T levels. T may be decreased by illness or certain medications, such as glucocorticoids or opiates. Sex hormone binding globulin may be decreased in patients with obesity, hypothyroidism, glucocorticoids, diabetes and nephrotic syndrome. Sex hormone binding globulin may be increased in aging, hyperthyroidism, liver disease, use of anticonvulsants or estrogens, human immunodeficiency virus infection, and porphyria [37].

T levels are alternatively described with several different units. Various publications and laboratories may express T concentrations either in pmol or nmol/l or in pg or ng/ml in the international community. A conversion factor of 0.2884 converts pmol or nmol/l into pg or ng/ml, respectively, and 3.467 converts pg or ng/ml into pmol or nmol/l [20]. The most common unit for T levels in the USA is ng/dl. A conversation factor of 100 converts ng/ml into ng/dl.

In 2005, the International Society for the Aging Male, the International Society of Andrology and the European Association of Urology established consensus recommendations to guide clinical practice regarding normal and abnormal T levels. Allowing for appropriate adjustments given specific laboratory references, total T above 346 ng/dl is normal and does not require supplementation, total T below 231 ng/dl is abnormal and often requires supplementation, and patients with intermediate levels may benefit from a trial of supplementation [33]. A common threshold for defining low T is 300 ng/dl because several studies have demonstrated that symptoms of hypogonadism are more likely to present below this threshold [22, 38].

The Endocrine Society provided a clinical practice guideline for the laboratory evaluation of hypogonadism in 2010 [28]. Blood samples for the evaluation of low total T should be obtained in the morning, preferably prior to 11 a.m., when patients are not experiencing concurrent illness. Obtaining a sample in the morning may be less important in older men, who have a blunted diurnal T variation [39]. A result of low total T should be confirmed with repeat test because up to 30 % of men have normal values on repeat analysis [40]. Free or bioavailable T levels should be calculated if total T is close to the lower limit of the reference range or if abnormalities are suspected in sex hormone binding globulin levels. Determination of luteinizing hormone (LH) may be further employed in the setting of low T to distinguish between primary and secondary hypogonadism. High LH indicates primary hypogonadism with testicular failure, and a karyotype to assess for a genetic condition such as Klinefelter syndrome may be warranted. Low or low-normal LH indicates secondary hypogonadism with an abnormality of the hypothalamic–pituitary–gonadal axis, and a prolactin level with or without cranial imaging may be warranted.

Role of Testosterone in the Physiology of Erections

An erection is a complex neurovascular event that is highly influenced by hormonal factors. The erectile pathway begins with parasympathetic signaling triggered by reflexogenic or psychogenic signals that lead to nitric oxide (NO) release causing vasodilation and engorgement, which in turn compresses penile venules and maintains tumescence [41].

T affects multiple points of the erectile pathway, as displayed in Fig. 7.1, including the central and peripheral nervous system as well as the penile vasculature and architecture as demonstrated in multiple rat and rabbit animal studies.

Within the central nervous system, T acts on the hypothalamic pre-optic area and arcuate nucleus in addition to the amygdala [42]. These centers are involved in sexual desire and libido [43].

Within the peripheral nervous system, T leads to increases in postganglionic neurons in the penis. Further neuron density facilitates corporal vascular relaxation through increases in NO during an erectile response. Following castration, T replacement has been shown to increase NO synthase containing nerve fibers in the rat penis [44].

Within the penis, T causes an increase in the NO synthase activity of the trabecular artery endothelium [45]. T depletion led to a reduction in NO synthase activity by 45 %, which was normalized by T replacement [46]. Enhanced NO synthesis leads higher NO levels and more efficient smooth muscle relaxation to help generate erections. Of note, however, some evidence supports an anti-erectile role for T through up-regulation of phosphodiesterase 5 (PDE5) expression and increase in cyclic guanosine monophosphate degradation (cGMP) [47]. These results have been contested and thought to possibly result from decreased smooth muscle content in the setting of low T [48]. Decreases in T promote subtunical architectural changes from smooth muscle apoptosis and collagen deposition [49]. These processes cause fibrosis that limits distensibility and contributes to venous leak, which impairs erection turgidity.

Human studies, though indirect and more limited, also support a role for T in the erection mechanism. The cutaneous vasodilatory effects of T were first demonstrated in 1939 [50]. More recently, T has been shown to acutely increase coronary artery blood flow in patients with coronary artery disease [51] and, in a placebo-controlled trial, to increase brachial artery vasodilation in eugonadal men with atherosclerosis [52]. Androgen receptors have been identified in the human corpus cavernosum [53]. Another study found a direct relationship between free T and cavernosal vasodilation on color Doppler ultrasonography in 52 eugonadal men [54]. Forays into the investigation of T's role in the brain centers of sexual function are quite preliminary. However, one study demonstrates activation of the hypothalamic sexual function centers during arousal on positron emission tomography that temporally correlate with increases in serum T levels [55].

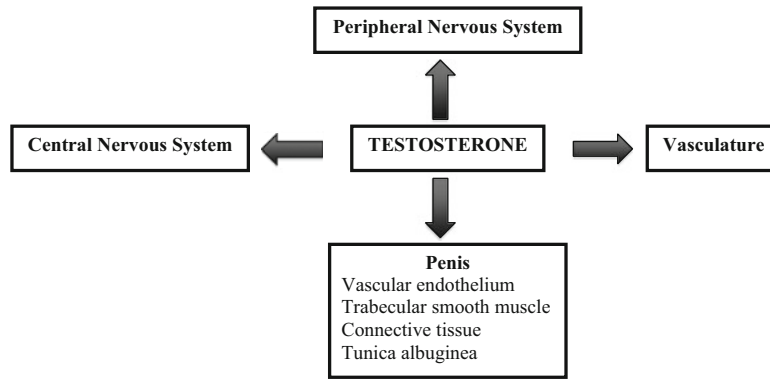

Fig. 7.1 Testosterone targets in erectile function

Association Between Testosterone and Sexual Function in Human Studies

T is required for pubertal virilization of the genitals and acquisition of adult sexual behaviors. Sufficient T is clearly important for normal libido. Placebo-controlled trials have demonstrated that both sexual desires and arousal are dependent on T [56, 57]. Large population studies have confirmed these findings. The Massachusetts Male Aging Study found a significant inverse association between low T and sexual desire with hypoactive sexual desire noted in 50 and 37 % of men with total T less than 200 ng/dL and less than 300 ng/dL, respectively [58]. It does appear that the blunting of libido is the principal sexual impact of hypogonadism. However, some data suggest at least a partial T-dependence on other aspects of male sexual function including erections.

The strongest evidence for the association between T and erections in humans comes from castration studies despite small study populations and the artificiality of acute androgen withdrawal. In populations of 38 and 16 patients respectively, between 58 % [59] and 75 % [60] of older men with prostate cancer treated with surgical or medical castration reported new onset complete ED following therapy despite prior normal erections. To eliminate the confounding of comorbidities, several studies have subjected young healthy participants to medical castration. Nine young men reported decreased libido and frequency of spontaneous erections with 6 weeks of medical castration that reversed with restoration of T levels [61]. A more recent study of 400 medically castrated men between the ages of 20 and 50 years demonstrate improvement in both sexual desire and erections with TRT [62]. The European Male Aging Study of men between the ages of 40 and 79 years represents one of the largest studies to demonstrate an association between low T and poor erections. The study found that low total T was associated with poor overall sexual function and that low free T was associated with ED. These associations were only demonstrated with T levels below 230 ng/dl [63].

This finding and other data indicate that a critical T threshold may exist which is below normal levels though still adequate for sexual function. T supplementation above this theoretical threshold would not further improve sexual function. The threshold likely varies between individuals. Men on TRT seem to request additional depot injection or pellet implantation due to bothersome symptoms around 260 ng/dl though levels between individuals ranged from 100 to 450 ng/dl [32, 64]. It seems that most sexual dysfunction occurs below 200 ng/dl and decreased frequency of nocturnal erections presents below 140–200 ng/dl whereas T levels above 450–600 ng/dl do not appear to further improve sexual function [65].

Testosterone Replacement Alone as Therapy for ED

The use of T supplementation in eugonadal men does not increase sexual interest or erectile function and should therefore not be used in the treatment of sexual dysfunction in general or ED in particular [66]. In a recent review of all randomized controlled trials, Isidori et al. found no sexual benefit to T supplementation in patients with T levels above 346 ng/dl [19]. Conclusions regarding the use of TRT in hypogonadal men for the purposes of treating ED are difficult to draw due to mixed results, lack of controls, small population sizes, and poor reporting of baseline T levels.

Several meta-analyses have examined the randomized controlled trials evaluating the use of TRT to treat ED. Due to the variability in the technique used to measure erectile function, the meta-analyses express overall treatment effect as standardized mean difference (SMD), which normalizes each study's outcome by the standard deviation of results. The earliest meta-analysis of 17 trials (656 patients) found a statistically significant positive effect of TRT in men with T levels below 288 ng/dl with a 1.8 SMD [67]. Another meta-analysis of 17 trials (862 patients) found a small benefit to TRT in the erectile function of hypogonadal men that was not statistically

significant overall but did show a significant benefit in younger hypogonadal men with a 1.8 SMD [68]. A final meta-analysis of 15 trials failed to show any statistically significant difference in erectile function in hypogonadal men treated with TRT [69].

In 2014, Isidori et al. compiled 20 randomized controlled trials investigating the use of TRT as therapy for erectile dysfunction and 14 of those trials assessed its effect in hypogonadal men specifically. A beneficial effect of TRT on erectile function was found in ten of the 14 trials. Five of these trials in hypogonadal men provided data on International Index of Erectile Function (IIEF), and in these studies, the mean improvement from baseline IIEF was 39 % and additional 4.3 points [19].

Trials investigating the benefit of T supplementation on ED have varied widely in terms of duration of treatment. Some studies have indicated that short-term TRT produces beneficial effects on libido; however, longer-term TRT may be necessary to achieve benefits in terms of erectile function. One study found that 6 months or up to 1 year of TRT may be required for improvements in ED [70].

Some investigations have examined increasing endogenous T as opposed to treatment of hypogonadism with exogenous T. Medications such as clomiphene citrate, a selective estrogen receptor modulator, and anastrozole, an aromatase inhibitor, increase endogenous T levels without reducing gonadotropin levels. Use of these medications for treatment of hypogonadism is particularly important in men considering fatherhood because administration of exogenous T inhibits spermatogenesis through reducing gonadotropin secretion. A double-blinded placebo-controlled study by Guay et al. utilized a 2-month course of clomiphene citrate in hypogonadal men with ED and found a significant increase in nocturnal tumescence by 36 % among younger men specifically [71]. Several recent case series have demonstrated that the use of clomiphene citrate can lead to an improvement in many hypogonadal symptoms as well, though its effect on erections are variable [72–74].

Testosterone Replacement as Therapy for ED in Combination with PDE5 Inhibitors

Phosphodiesterase type-5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil, avanafil) have been conclusively demonstrated to improve erectile function in men with ED [75]. Given the frequent overlap between hypogonadism and ED, the use of TRT in combination with PDE5 inhibitors has naturally been explored. Interestingly, administration of PDE5 inhibitors without TRT in hypogonadal men leads to a small increase in T levels through an unclear mechanism. One randomized trial demonstrated an increase of 115 ng/dl in total T following 1 month of PDE5 inhibitor alone [76]. Spitzer et al. demonstrated no additional benefit in terms of erection quality to those men who responded to treatment with PDE5 inhibitors [76]. Proponents of combination argue, however, that TRT could improve the other elements of sexual function, such as libido, not significantly impacted by PDE5 inhibitors in hypogonadal men. The use of TRT in this context is controversial. Some evidence does support adding TRT to hypogonadal men who fail to adequately respond to PDE5 inhibitors. Shabsigh et al. found a statistically significant increase in IIEF scores among nonresponders to PDE5 inhibitors among hypogonadal men treated with TRT for 1 month, whose IIEF scores increased 2.3 points more than with placebo [77]. In a study of 173 hypogonadal men who failed to respond to tadalafil, Buvat et al. demonstrated a statistically significant increase in erectile function based on IIEF scores for PDE5 inhibitor nonresponders with a baseline T level less than 300 ng/dl [78].

Society Recommendations for Hypogonadism Screening in All ED Patients

Debate persists among specialty societies regarding screening for hypogonadism in patients that present with ED given the occasionally unreliable laboratory evaluation of hypogonadism and the lack of studies demonstrating definitive benefit to

TRT in this patient population. A meta-analysis of the cost-effectiveness of screening men with ED for hypogonadism was inconclusive [69].

Several organizations recommend universal screening in ED patients. The Princeton III Consensus for the management of ED and cardiovascular disease from 2012 recommends a total T level drawn prior to 11 a.m. in all men presenting with organic ED and especially in those men who have failed to respond to PDE5 inhibitors [16]. The European Association of Urology Guidelines on Male Sexual Dysfunction from 2014 recommend a morning total T level with follow-up assessment of bioavailable T, prolactin and luteinizing hormone if total T is low [79].

Other societies simply recommend selective screening. The American Urological Association Erectile Dysfunction Guideline from 2011 states that in the laboratory evaluation of ED including "testosterone level measurement…may be indicated in select patients" without further description [80]. The American College of Physicians Practice Guideline for the hormonal testing and pharmacologic treatment of ED from 2009 recommends measuring T only in ED patients with symptoms and physical findings of hypogonadism, such as decreased libido or testicular atrophy [81].

Potential benefits of universal screening and treatment of hypogonadal men with ED include determining treatable causes of hypogonadism, such as a pituitary tumor; detecting hypogonadism only presenting with subtle clinical manifestations; a clear effect on libido; possible improvement in erections especially in younger men and those patients who failed to respond to PDE5 inhibitors; and positive effects of TRT like decreases in obesity and insulin resistance as well as increases in bone density [24]. Potential risks of universal screening include over-diagnosis and treatment with additional financial costs and unclear clinical benefit to improve erections.

Therapy for Hypogonadism

Following the diagnosis of hypogonadism, conventional treatment typically relies on using exogenous T as replacement or supplementation. It is important to confirm that these patients are not actively trying to achieve a pregnancy or interested in immediate future fertility, as they may benefit from other agents to boost endogenous testosterone production while preserving spermatogenesis. Many different formulations of conventional TRT exist. These formulations include topical gels, transdermal patches, injections, implantable pellets, and buccal adhesives. Oral formulations of T are not approved in the USA. The pharmacokinetic profiles in addition to unique advantages and disadvantages of each formulation are illustrated in Table 7.2. According to the Endocrine Society Clinical Guideline from 2010, there are several common initial treatment regimens: 150–200 mg intramuscular injection once every 2 weeks, one to two 5 mg patches applied nightly, or 5–10 mg gel applied daily [28]. The goal of replacement therapy is to elevated total T into the mid-normal range.

TRT is contraindicated in certain patients. TRT should be avoided in patients with active breast or prostate cancer and prostate-specific antigen (PSA) level greater than 4 ng/ml or greater than 3 ng/ml in men with risk factors such as African-American race or family history because exogenous T may stimulate cancer growth [82]. T may also worsen sleep apnea and heart failure, and therefore it is contraindicated in patients with severe obstructive sleep apnea and uncontrolled congestive heart failure [28]. Furthermore, TRT has been shown to increase hematocrit, particularly when using parental formulations, and for that reason, patients undergoing TRT should have a complete blood count (CBC) as part of their monitoring protocol. Additionally, as expressed earlier, the use of exogenous testosterone is contraindicated in anyone interested in achieving a pregnancy in the short-term as it has been shown to suppress spermatogenesis. In a study by the World Health Organization, 271 normal men received T enanthate 200 mg weekly; after a period of 6 months, 75 % of these men were azoospermic. Even though 86 % of these men were able to return to have a normal sperm concentration after 3.7 months of cessation, only 46 % returned to their baseline sperm concentration at that time

Table 7.2 Options for testosterone replacement therapy

Name	Route	Starting dose	Frequency	Comments
Androgel, 1.62 % Gel	Topically to each shoulder/upper arm	2 pumps (1 to each shoulder)	Daily	Mimics physiologic dosing Transfer risk if gel not completely dry
Axiron	Topically to underarms	2 pumps (1 to each underarm)	Daily	Mimics physiologic dosing Transfer risk if gel not completely dry
Fortesta	Topically to inner thighs	4 pumps (2 to each thigh)	Daily	Mimics physiologic dosing Transfer risk if gel not completely dry
Testim 1 %	Topically to each shoulder/upper arm	1 tube (divide among shoulders)	Daily	Mimics physiologic dosing Transfer risk if gel not completely dry
Androderm, 4 g patch	Topical patch	1 patch	Daily	Mimics physiologic dosing May cause contact dermatitis
Testopel	Subdermally placed in fat (usually in buttocks)	10–12 pellets	Every 3.5–6 months	Sustained release, long-acting Small local procedure May cause mild site discomfort
Testosterone injections (standard)	Intramuscular injections	300 mg	300 mg every 3 weeks (or 200 mg every 2 weeks, 100 mg every week, or 60 mg twice weekly)	Long-acting Does not mimic physiologic levels, creates peaks and troughs
Aveed (testosterone long-acting injection)	Intramuscular injections	750 mg	750 mg, 5 injections per year	Long-acting Does not mimic physiologic levels, fewer peaks and troughs

[83]. Lastly, some studies suggest that TRT worsens lower urinary tract symptoms so it is also contraindicated in patients with severe voiding dysfunction (International Prostate Symptom Score greater than 19). This assertion has been challenged by Pearl and colleagues; no increase in voiding bother was demonstrated in a retrospective case series following TRT initiation [84].

Theoretical safety concerns regarding the use TRT involve stimulating the incidence or progression of prostate cancer and contributing to cardiovascular events. In terms of prostate cancer risk, although castration levels of androgen deprivation have been clearly shown to impede prostate cancer growth, the converse of T replacement leading to prostate cancer development has not been shown. In a large comparison of men with incidentally discovered prostate cancer with matched controls, endogenous T concentrations had no effect on prostate cancer risk [85]. The saturation model proposed by Morgentaler and Traish hypothesizes that prostatic growth requires a sub-physiologic level of T above which further increases in T do not contribute to growth [86]. Indeed, the International Society for Sexual Medicine (ISSM) reported in 2013 that, based on meta-analysis of randomized controlled trials, no

evidence exists to support an association between TRT and prostate cancer risk [87]. However, the ISSM guidelines also state that appropriate screening prior to the initiation of TRT is important based on expert opinion due to the risk of supporting untreated prostate cancer growth [87]. For men who have been successfully treated for localized prostate cancer, most guidelines support the safety of TRT after a reasonable interval following treatment. The 2012 European Association of Urology guidelines recommend waiting 1 year following treatment to initiate TRT in the absence of biochemical recurrence and history of Gleason score over 7 [88]. Few studies have examined the effects of TRT in men previously treated for prostate cancer though. Isidori et al. performed a systematic analysis of five case series of men on TRT following radical prostatectomy and found that only four out of 179 men developed biochemical recurrence (2.2 %) within 2 years on TRT [19].

More recently, three studies have found an association between TRT and cardiovascular events, including stroke, heart attack, and death, which has caused the FDA to initiate an investigation into the cardiovascular safety of TRT [6–8]. In a post hoc analysis, Basaria et al. found 23 cardiovascular-related events in elderly men receiving TRT to increase muscle strength compared with four events in a control arm for an adjusted odds ratio of 5.8 [6]. Vigen et al. performed a retrospective review of veterans and found that the rate of heart attack, stroke or death was 25.7 % in men on TRT compared with 19.9 % in control men through highly complex statistical adjustment [7]. Finally, Finkle et al. demonstrated that men receiving a T prescription were 1.36 times more likely to have a heart attack within 90 days of the prescription compared to those men receiving a sildenafil prescription [8]. The statistical validity of these studies documenting increased risk has been extensively questioned, however [10]. Some research has led to theories to explain a possible harmful mechanism in TRT. T may increase thromboxane A2 density and platelet aggregation [89]. TRT may increase blood viscosity with an associated mean hemoglobin increase of 0.8 g/dl [90].

Many studies have actually demonstrated a detrimental effect of low T with increases in obesity, insulin resistance, and dyslipidemia [91]. Low T has also been associated with higher mortality. Androgen deprivation therapy for men with prostate cancer increases the risk of heart attack, stroke, and sudden cardiac death with a hazard ratio around 1.3 [92]. Another meta-analysis of 12 studies revealed a 35 % increase in all-cause mortality for a decrease in two standard deviations of total T relative to the general population [93]. Furthermore, a large body of literature supports a possible protective effect of TRT including decreasing weight [11], insulin resistance [12], and heart attacks [13]. Shores et al. found that TRT decreased overall mortality with a hazard ratio of 0.61 among a population of veterans taking T supplementation as part of routine care compared with control patients [14].

No study has yet examined the possible cardiovascular risks of TRT within the context of a randomized placebo-controlled trial. In the absence of a randomized placebo-controlled trial and given the competing findings in the available literature, the exact nature of the cardiovascular effects of TRT remains to be fully elucidated. Seftel et al. proposed a conservative approach to the management of patients considering TRT initiation in the setting of elevated baseline cardiovascular risk [94]. The Princeton III Consensus Recommendations [16] may be used to stratify patients according to baseline cardiovascular risk to determine if further cardiac clearance or referral to a cardiologist is necessary before starting TRT.

Close follow-up is required after initiating TRT to ensure appropriate response, adjust dosing requirements, and monitor for negative effects. According to the Endocrine Society guidelines, men should return to the office about 3–6 months after starting TRT and annually thereafter to assess for symptom response and any adverse reactions [28]. Total T should be checked at the initial return visit, with the goal to increase the T level to mid-normal range, and annually thereafter. Hematocrit should be checked at baseline, initial return visit, and annually thereafter with hematocrit above 54 %

as an indication to cease therapy and perform therapeutic phlebotomy. Bone densitometry scan should be obtained at baseline in hypogonadal men due to fracture risk and about once every 2 years thereafter. Blood glucose and lipid profile should be assessed at baseline and annually thereafter. PSA should be obtained and digital rectal examination should be performed at baseline, initial return visit, and annually thereafter in men over 40 years old or men with a baseline PSA over 0.6 ng/ml. PSA velocity over 1.4 ng/ml in 12 months or changes in digital rectal examination should prompt further evaluation with a prostate needle biopsy in men under 75 years of age.

Algorithms for Testosterone Replacement in Hypogonadal Men with ED

Men complaining of ED and symptoms of hypogonadism should be evaluated with a morning total T level and a confirmatory test if initial evaluation reveals low T. If found to be eugonadal with total T above 300 ng/dl, then ED treatment should proceed in standard fashion with PDE5 inhibitors and other methodologies without the incorporation of TRT. For men with severe hypogonadism with total T below 200 ng/dl, treatment should begin with TRT in the absence of contraindications to T supplementation. Response to TRT should be assessed in 3–6 months and inclusion of a PDE5 inhibitor should be considered in the setting of inadequate response. Men planning on fatherhood within the upcoming 12 months should utilize a regimen of clomiphene citrate or a combination of TRT with human chorionic gonadotropin (HCG) to ensure continued spermatogenesis during therapy. For men with borderline hypogonadism with total T between 200 and 300 ng/dl, treatment should be stratified based on age. Younger men should be started on TRT after a thorough discussion regarding the effects of conventional TRT and their fertility potential. These men considering fatherhood should avoid simple traditional exogenous T supplementation and consider an agent to boost endogenous testosterone production. Older men and those with potential cardiovascular comorbidities should be started on a PDE5 inhibitor. Failure to improve symptoms after 3–6 months of therapy should prompt the addition of a PDE5 inhibitor to the younger group and TRT to the older group.

Other Hormones and ED

Luteinizing Hormone (LH)

LH is critical to the endogenous production of T and a fundamental part of the hypothalamic–pituitary–gonadal axis. LH is released from the pituitary gland in response to gonadotropin releasing hormone from the hypothalamus. LH directly stimulates Leydig cells in the testicles to produce T. LH helps to distinguish between primary and secondary causes of hypogonadism. Elevated LH indicates a primary failure of the testicles to produce T while a low or low-normal LH corresponds to insufficiencies localized to the pituitary or hypothalamus.

Prolactin

Prolactin is secreted by the pituitary gland. Hyperprolactinemia can be caused by tumors within the pituitary. In men, the most common presenting symptoms of hyperprolactinemia are decreased libido and ED [95]. Hyperprolactinemia is a rare cause of ED overall, however, and only accounts for about 1 % of ED [96]. Serum prolactin should be obtained in younger men with hypogonadism and ED and especially in those with visual disturbances or gynecomastia. Head MRI should be ordered to assess for pituitary masses in those patients with hyperprolactinemia. Hyperprolactinemia is treated with cabergoline, a dopamine agonist, with surgical resection rarely performed. Cabergoline therapy for hyperprolactinemia resulted in improvement of erectile function in 97 % of men compared with 13 % of controls after 6 months [97].

Estradiol

Estradiol, an estrogen, can result from the peripheral conversion of T by aromatase especially in adipose tissue. Elevated estradiol levels contribute to decreases in LH and T as well as increases in sex hormone binding globulin, which may further hypogonadal symptoms [98]. TRT may lead to higher estradiol levels due to increased T and aromatase-mediated conversion. In practice, elevated estradiol levels can lead to gynecomastia and breast tenderness but additional negative sexual side effects are not well supported [99]. Bothersome breast enlargement and pain may be treated with an aromatase inhibitor, such as anastrozole.

Thyroid Hormone

Sexual dysfunction is commonly found in patients with significant hyperthyroidism or hypothyroidism though ED is rarely the presenting symptom. Hyperthyroidism may lead to increased adrenergic tone that inhibits cavernosal smooth muscle relaxation as well as elevations in estrogen and sex hormone binding globulin. Hypothyroidism may contribute to hyperprolactinemia. ED resolves with treatment of the underlying thyroid disorder. Screening tests with thyroid stimulating hormone for patients with ED are unnecessary in the absence of classic manifestations of thyroid disorders [100].

Future Directions

A set of ongoing randomized trials sponsored by the National Institutes of Health will provide more data to address current controversies regarding TRT including its impact on erectile function and cardiovascular risk. The Testosterone Trial in Older Men is comprised of seven separate randomized, placebo-controlled, double-blinded trials. The trials will obtain information on the impact of TRT on sexual function, physical function, vitality, cognition, anemia, cardiovascular health, and bone density. About 800 men over 65 years old with low T were randomized to transdermal TRT or placebo gel for 1 year. Changes in sexual function will be assessed through patient responses to validated sexual function questionnaires. Changes in cardiovascular health will be assessed with alterations in plaque burden visualized on computerized tomographic angiography. These trials were initiated in November 2009 and have an estimated completion date of July 2015 [101].

Conclusions

Most recommendations support screening men with ED for hypogonadism, particularly among those men presenting with any additional hypogonadal symptoms. T clearly has a substantial influence on libido and energy but may have only a mild effect on erections. Men with very low T or younger men should be initially treated with TRT in effort to improve erectile function. Older men and those with borderline hypogonadism or comorbidities should be started on a PDE5 inhibitor with later addition of TRT in the setting of an insufficient response. Eugonadal men with ED should not be treated with TRT.

References

1. Baillargeon J, Urban RJ, Ottenbacher KJ, et al. Trends in androgen prescribing in the United States, 2001 to 2011. JAMA Intern Med. 2013;173:1465–6.
2. Handelsman DJ. Global trends in testosterone prescribing, 2000–2011: expanding the spectrum of prescription drug misuse. Med J Aust. 2013;19:548–51.
3. Garnick MB. Testosterone replacement therapy faces FDA scrutiny. JAMA. 2015;313:563–4.
4. Ko EY, Siddiqi K, Brannigan RE, et al. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. J Urol. 2012;187:973–8.
5. American Urological Association: five things that physicians and patients should question. In: Choosing Wisely; 2013. https://www.auanet.org/common/pdf/practices-resources/quality/choosing-wisely/Five-Questions.pdf. Accessed 14 Feb 2015.

6. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. NEJM. 2010;363:109–22.
7. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013;310:1829–36.
8. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014;9:1–7.
9. Tavernise S. F.D.A. panel backs limits on testosterone drugs. The New York Times; 2014. http://www.nytimes.com/2014/09/18/health/testosterone-drugs-fda.html?_r=0. Accessed 14 Feb 2015.
10. Morgentaler A. Testosterone, cardiovascular risk, and hormonophobia. J Sex Med. 2014; 11:1362–6.
11. Kalinchenko SY, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol. 2010;73:602–12.
12. Jones TH, Arver S, Behre HM, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care. 2011;34:828–37.
13. Baillargeon J, Urban RJ. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother. 2014;48:1138–44.
14. Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab. 2012;97:2050–8.
15. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset, and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol. 2003;44:360–4.
16. Nehra A, Jackson G, Miner M, et al. The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87:766–78.
17. Guay AT, Traish A. Testosterone deficiency and risk factors in the metabolic syndrome: implications for erectile dysfunction. Urol Clin N Am. 2011;38: 175–83.
18. Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. NEJM. 2010;363:123–35.
19. Isidori AM, Buvat J, Corona G, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment—a systematic review. Eur Urol. 2014;65:99–112.
20. Buvat J, Jaoude GB. Significance of hypogonadism in erectile dysfunction. World J Urol. 2006;24: 657–67.
21. Mulligan T, Frick MF, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract. 2006;60:762–9.
22. Hall SA, Esche GR, Araujo AB, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab. 2008;93:3870–7.
23. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychological correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151:54–61.
24. Mikhail N. Does testosterone have a role in erectile function? Am J Med. 2006;119:373–82.
25. Kohler TS, Kim J, Feia K, et al. Prevalence of androgen deficiency in men with erectile dysfunction. Urology. 2008;71:693–7.
26. Buvat J, Lemaire A. Endocrine screening in 1022 men with erectile dysfunction: clinical significance and cost-effective strategy. J Urol. 1997;158:764–7.
27. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2002;87:589–98.
28. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol. 2010;95: 2536–59.
29. Tancredi A, Reginster JY, Schleigh F, et al. Interest of the androgen deficiency in aging males (ADAM) questionnaire for the identification of hypogonadism in elderly community-dwelling male volunteers. Eur J Endocrinol. 2004;151:355–60.
30. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49:1239–42.
31. Matsumoto AM, Bremner WJ. Serum testosterone assays—accuracy matters. J Clin Endocrinol Metab. 2004;89:520–4.
32. Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. J Clin Endocrinol Metab. 2004;89:3813–7.
33. Nieschlag E, Swerdloff R, Behre HM, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM, and EAU recommendations. Eur Urol. 2005;48:1–4.
34. Wang C, Catlin DH, Demers LM, et al. Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. J Clin Endocrinol Metab. 2004;89:534–43.
35. Mohr BA, Guay AT, O'Donnell AB, et al. Normal, bound, and nonbound testosterone levels in normally ageing men: results from the Massachusetts male aging study. Clin Endocrinol. 2005;62:64–73.
36. Earle CM, Stuckey BG. Biochemical screening in the assessment of erectile dysfunction: what tests decide future therapy? Urology. 2003;62:727–31.

37. Elin RJ, Winters SJ. Current controversies in testosterone testing: aging and obesity. Clin Lab Metab. 2004;24:119–39.
38. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006;91:4335–43.
39. Welliver R, Wiser H, Brannigan R, et al. Validity of midday total testosterone levels in older men with erectile dysfunction. J Urol. 2014;192:165–9.
40. Brambilla S, O'Donnell AB, Matsumoto AM, et al. Intraindividual variation in levels of serum testosterone and other reproductive and adrenal hormones in men. Clin Endocrinol. 2007;67:853–62.
41. Hockenberry MS, Masson P. Erectile dysfunction in the elderly. Curr Geri Rep. 2015;4:33–43.
42. Angelback JH, DuBrul EF. The effect of neonatal testosterone on specific male and female patterns of phosphorylated cystosolic proteins in the rat preoptic-hypothalamus, cortex and amygdala. Brain Res. 1983;264:277–83.
43. Hull EM, Lorrain DS, Du J, et al. Hormone-neurotransmitter interactions in the control of sexual behavior. Behav Brain Res. 1999;105:105–16.
44. Baba K, Yajima M, Carrier S, et al. Delayed testosterone replacement restores nitric oxide synthase-containing nerve fibres and the erectile response in rat penis. BJU Int. 2000;85:953–8.
45. Traish AM, Kim N. The physiological role of androgens in penile erection: regulation of corpus cavernosum structure and function. J Sex Med. 2005;2:759–70.
46. Chamness SL, Ricker DD, Crone JK, et al. The effect of androgen on nitric oxide synthase in the male reproductive tract of the rat. Fertil Steril. 1995;63:1101–7.
47. Zhang XH, Morelli A, Luconi M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. Eur Urol. 2005;47:409–16.
48. Yang R, Huang YC, Lin G, et al. Lack of direct androgen regulation of PDE5 expression. Biochem Biophys Res Commun. 2009;380:758–62.
49. Traish AM, Toselli P, Jeong SJ, et al. Adipocyte accumulation in penile corpus cavernosum of the orchiectomized rabbit: a potential mechanism for veno-occlusive dysfunction in androgen deficiency. J Androl. 2005;26:242–8.
50. Edwards E, Hamilton J, Duntley S. Testosterone propionate as a therapeutic agent in patients with organic disease of peripheral vessels. N Engl J Med. 1939;220:865.
51. Webb CM, McNeill JG, Hayward CS, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary artery disease. Circulation. 1999;100:1690–6.
52. Kang S, Jang Y, Kim Y, et al. Effect of oral administration of testosterone on brachial artery vasoreactivity in men with coronary artery disease. Am J Cardiol. 2002;89:862–4.
53. Schultheiss D, Badalyan R, Platz A, et al. Androgen and estrogen receptors in the human corpus cavernosum penis immunohistochemical and cell culture results. World J Urol. 2003;21:320–4.
54. Aversa A, Isidori AM, DeMartino MU, et al. Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. Clin Endocrinol. 2000;53:517–22.
55. Storelu S, Gregoire M, Gerard D, et al. Neuroanatomical correlates of visually evoked sexual arousal in human males. Arch Sex Behav. 1999;28:1–21.
56. Steidle C, Schwartz S, Jacoby K, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab. 2003;88:2673–81.
57. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab. 2000;85:839–53.
58. Travison TG, Araujo AB, Morley JE, et al. The relationship between libido and testosterone in aging men results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2006;91:2509–13.
59. Ellis WJ, Grayhack JT. Sexual function in aging males after orchiectomy and estrogen therapy. J Urol. 1963;89:895–9.
60. Greenstein A, Plymate SR, Katz PG. Visually stimulated erection in castrated men. J Urol. 1995;153:650–2.
61. Bagatell CJ, Heiman JR, Rivier JE, et al. Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. J Clin Endocrinol Metab. 1994;78:711–6.
62. Finklestein JS, Lee H, Burnett-Bowie SA, et al. Gondal steroids and body composition, strength, and sexual function in men. N Engl J Med. 2013;369:1011–22.
63. O'Connor DB, Lee DM, Corona G, et al. The relationships between sex hormones and sexual function in middle-aged and older European men. J Clin Endocrinol Metab. 2011;96:E1577–87.
64. Gooren LJ. Androgen levels and sex functions in testosterone-treated hypogonadal men. Arch Sex Behav. 1987;16:463–73.
65. Carani C, Bancroft J, Granata A, et al. Testosterone and erectile function, nocturnal penile tumescence and rigidity, and erectile response to visual erotic stimuli in hypogonadal and eugonadal men. Psychoneuroendocrinology. 1992;17:647–54.
66. Anderson RA, Bancroft J, Wu FC. The effects of exogenous testosterone on sexuality and mood of normal men. J Clin Endocrinol Metab. 1992;75:1503–7.
67. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol. 2005;63:381–94.

68. Bolona ER, Uraga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007; 82:20–8.
69. Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments of erectile dysfunction: a systematic review and meta-analysis. Ann Intern Med. 2009;151:650–1.
70. Saad F, Aversa A, Isidori AM, et al. Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol. 2011;165:675–85.
71. Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. J Clin Endocrinol Metab. 1995;80:3546–52.
72. Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. J Sex Med. 2010;7:269–76.
73. Katz DJ, Nabulsi O, Tal R, et al. Outcome of clomiphene citrate treatment in young hypogonadal men. BJU Int. 2012;110:573–8.
74. Moskovic DJ, Katz DJ, Akhavan J, et al. Clomiphene citrate is safe and effective for long-term management of hypogonadism. BJU Int. 2012;110:1524–8.
75. Jannini EA, Isidori AM, Gravina GL, et al. The ENDOTRIAL study: a spontaneous, open-label, randomized, multicenter, crossover study on the efficacy of sildenafil, tadalafil, and vardenafil in the treatment of erectile dysfunction. J Sex Med. 2009;6:2547–60.
76. Spitzer M, Basaria S, Travison TG, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. Ann Intern Med. 2012;157: 681–91.
77. Shabsigh R, Kaufman JM, Steidle C, et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to tadalafil alone. J Urol. 2004;172:658–63.
78. Buvat J, Montorsi F, Maggi M, et al. Hypogonadal men nonresponders to PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1 % hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med. 2011;8:284–93.
79. Hatzimouratidis K, Eardley I, Giuliano F, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Arnhem: European Association of Urology; 2014. http://uroweb.org/guideline/male-sexual-dysfunction/. Accessed 14 Feb 2015.
80. Montague DK, Jarow JP, Broderick GA, et al. Erectile dysfunction guideline; 2011. AUA. https://www.auanet.org/common/pdf/education/clinical-guidance/Erectile-Dysfunction.pdf. Accessed 14 Feb 2015.
81. Qaseem A, Snow V, Denberg TD, et al. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2009;15:639–49.
82. Fowler JE, Whitmore WF. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol. 1981;126:372–5.
83. World Health Organization Task Force. World Health Organization Task Force on methods for regulation of male fertility. contraceptive efficacy of testosterone-induced azoospermia in normal men. Lancet. 1990;336:955–9.
84. Pearl JA, Berhanu D, Francois N, et al. Testosterone supplementation does not worsen lower urinary tract symptoms. J Urol. 2013;190:1828–33.
85. Roddam AW, Allen NE, Appleby P. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst. 2008;100:170–83.
86. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol. 2009;55:310–20.
87. Buvat J, Maggi M, Guay A. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med. 2013;10:245–84.
88. Dohle GR, Arver S, Bettochi S. Guidelines on male hypogonadism. Arnhem: European Association of Urology; 2012. http://uroweb.org/guideline/male-hypogonadism/. Accessed 14 Feb 2015.
89. Ajayi AA, Mathur R, Halushka PV. Coronary heart disease/myocardial infarction: testosterone increases human platelet thromboxane A sub 2 receptor density and aggregation responses. Circulation. 1995;91:2742–7.
90. Fernandez-Balsells MM, Murad MH, Lane M, et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010;95:2560–75.
91. Jones TH. Testosterone deficiency: a risk factor for cardiovascular disease? Trends Endocrinol Metab. 2010;21:496–503.
92. Keating NL, O'Malley J, Freedland SJ, et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010;102:39–46.
93. Araujo AB, Dixon JM, Suarez EA, et al. Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011;95:3007–19.
94. Seftel AD. Does testosterone increase the risk of a cardiovascular event? Yes. J Urol. 2014;192:13–5.

95. Bhasin S, Enzlin P, Coviello A, et al. Sexual dysfunction in men and women with endocrine disorders. Lancet. 2007;369:597–611.
96. Delavierre D, Girard P, Peneau M, et al. Should plasma prolactin assay be routinely performed in the assessment of erectile dysfunction? Report of a series of 445 patients. Prog Urol. 1999;9:1097–101.
97. De Rosa M, Zarrilli S, Vitale G, et al. Six months of treatment with cabergoline restores sexual potency in hyperprolactinemic males: an open longitudinal study monitoring nocturnal penile tumescence. J Clin Endocrinol Metab. 2004;89:621–5.
98. Morales A, Heaton JP. Hypogonadism and erectile dysfunction: pathophysiological observations and therapeutic outcomes. BJU Int. 2003;92:896–9.
99. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med. 2004;350:482–92.
100. Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metab. 2005;90:6472–9.
101. Clinicaltrials.gov. The testosterone trial in older men. 2008. https://www.clinicaltrials.gov/ct2/show/NCT00799617. Accessed 14 Feb 2015.

Effects of Lifestyle Changes and Testosterone Therapy on Erectile Function

8

Abdulmaged M. Traish and James T. Trussler

Introduction

Sexual function is an integral part of overall health and has critical and important implications for an individual's quality of life and well-being. Erectile function (EF) is a complex neurovascular process modulating physiological and biochemical pathways, requiring an intact and functional central and peripheral nervous systems, as well as a healthy vascular system. In this chapter, we discuss the impact of lifestyle and behavioral changes, such as physical activity, exercise and diet, reduction in alcohol consumption, and smoking cessation on EF. We also address issues pertaining to lifestyle changes and its relationship to obesity, diabetes, cardiovascular disease (CVD), hypogonadism, and how such comorbidities influence EF. Since testosterone deficiency (hypogonadism; TD) contributes to fatigue, reduced vigor and vitality, reduced motivation and energy, and contributes to vascular risk factors, we also discuss the effects of testosterone therapy on improving the function of the vascular system, weight loss (WL), improving mood, increasing energy and vigor, and ameliorating metabolic syndrome (MetS) components and improving overall sexual function and erectile physiology.

"Man survives earthquakes and all the tortures of the soul, but the most tormenting tragedy is the tragedy of the bedroom." Tolstoy

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Physiology of Erectile Function (EF) and Pathophysiology of Erectile Dysfunction (ED)

EF is a complex neurovascular physiological process, which involves interplay among neural, vascular, hormonal, and psychological factors, as well as the integrity of the vascular bed of the penis [1]. Disruption of such mechanisms contributes to ED [2]. EF requires intact, functioning penile vascular tissues and perineal and ischiocavernous muscles that support the proximal penis. Sufficient arterial inflow and trapping of blood within the cavernosal bodies is critical for the development of increasing pressure and volume expansion (*veno-occlusion*). In addition to arterial blood pressure, contraction of the perineal and ischio-cavernous muscles enhances penile rigidity. The veno-occlusive mechanism depends on the integrity of neural, vascular, and endocrine systems, as well as on the fibroelastic properties of the cavernosal tissue [1, 2].

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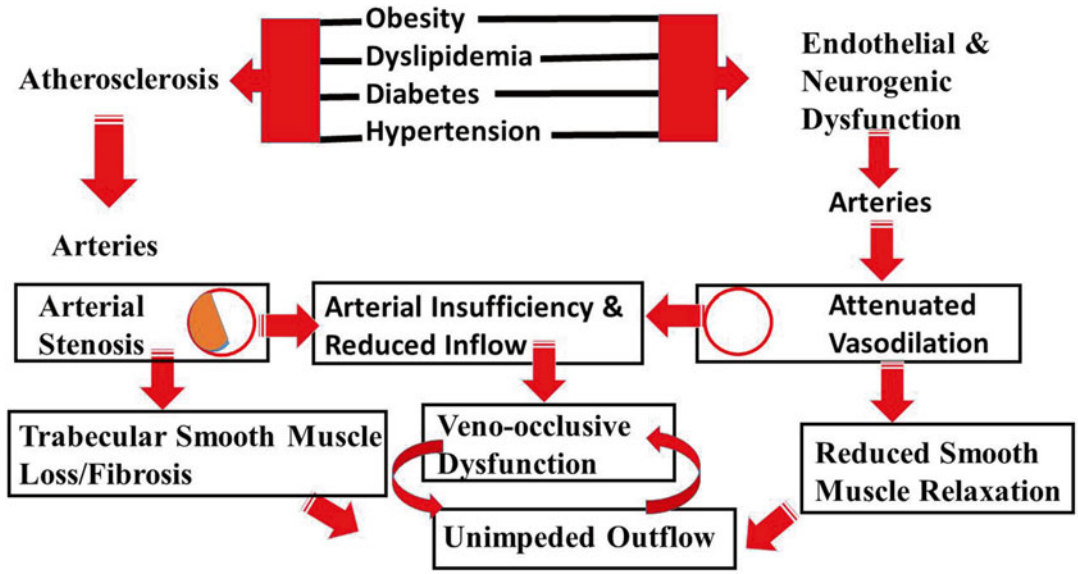

Fig. 8.1 Pathophysiology of erectile dysfunction

Following sexual stimulation, release of nitric oxide (NO) from penile non-adrenergic-non-cholinergic (NANC) nerves and the endothelium activates guanylyl cyclase and induces synthesis of intracellular cGMP synthesis in erectile tissue trabecular smooth muscle cells. Increased cGMP levels reduce intracellular Ca^{2+} concentrations, inhibiting smooth muscle contractility and thereby initiating erection. Phosphodiesterase type 5 (PDE type 5) is the predominant enzyme in the corpus cavernosum responsible for cGMP hydrolysis in trabecular smooth muscle. Activation of PDE type 5 terminates NO-induced, cGMP-mediated smooth muscle relaxation, resulting ultimately in restoration of basal smooth muscle contractility and penile flaccidity. Several other mechanisms are also involved in penile smooth muscle contractility and play a role in erectile physiology [3, 4]. For brevity sake, these mechanisms will not be discussed further in this chapter.

During erection, the penis acts as a capacitor, accumulating blood under pressure [1, 2, 5]. This hemodynamic process, known as veno-occlusive function, depends on several distinct physiological mechanisms. These include (1) sexual stimulation, which activates the parasympathetic non-adrenergic, non-cholinergic (NANC) nerves, releasing nitric oxide (NO); (2) dilation of cavernosal arteries and the helicine arterioles of the penis, providing flow and pressure to the corpora; (3) the relaxation of the trabecular smooth muscle, allowing expansion of the lacunar spaces and trapping of blood by compression of the draining venules; and (4) compliance of the tunica albuginea and the connective tissue matrix, permitting adequate compression of the subtunical venules and reducing blood outflow [1, 6–9]. When the trabecular smooth muscle is fully relaxed, the intracavernosal pressure is dependent on the cavernosal arterial pressure and the tissue fibroelastic properties. Thus, tissue architecture plays an important role in veno-occlusive function, and any pathology that contributes to altering tissue architecture will result in veno-occlusive dysfunction [1–9].

As depicted in Fig. 8.1, the pathophysiology of erection is a result of host of factors that alters the neurogenic and vascular endothelium function as, well as the health and function of the trabecular smooth muscle of the cavernosal bodies. Diabetes, metabolic syndrome (MetS), obesity, hypertension, vascular disease, atherosclerosis, among others alter the function of the neurogenic signaling and endothelial function resulting in arterial insufficiency, reduced vasodilation, increased fibrosis, and impaired smooth muscle contractility with concomitant veno-occlusive dysfunction and ED [2, 5].

Corporeal veno-occlusive dysfunction is an important cause of organic ED and is characterized by the need for increased flow rates to maintain erection during clinical evaluation of ED [8–12]. Corporeal veno-occlusive dysfunction alone or combined with arterial disease is the hemodynamic abnormality resulting in no response to intracavernous pharmacotherapy [13–17]. The existence of concomitant arterial and sinus smooth muscle disease makes veno-occlusive dysfunction often difficult to diagnose and treat.

Risk Factors Contributing to ED

Cavernosal tissue from men with ED often exhibited reduced smooth muscle content and concomitant increase in connective tissue deposition. This may contribute to penile tissue fibrosis and decreasing tissue compliance, leading to veno-occlusive dysfunction [2]. Vascular disease is a common risk factor for organic ED attributed to impairment of arterial inflow, increased cavernosal fibrosis, and reduced cavernosal smooth-muscle relaxation [2, 18]. Vascular disease also contributes to endothelial dysfunction, which is closely linked to vascular ED [7]. A link between diabetes and ED has been suggested based on epidemiological evidence [19]. The prevalence of ED is approximately three times higher in diabetic men [20–22].

As depicted in Fig. 8.2, several risk factors contribute to ED. Physical inactivity, and poor diet are thought to contribute to ED via excessive weight gain and adiposity. Further, excessive alcohol consumption and/or smoking also contribute to ED via a host of mechanisms, yet to be explored fully. Obesity (Table 8.1) [23–35] diabetes, MetS, dyslipidemia (Table 8.2) [36–48] and cardiovascular disease are also risk factors for ED by contributing to insulin resistance, dyslipidemia, inflammation hyperglycemia and atherosclerosis [49–51].

An inverse association between physical activity and ED has been reported [25, 52, 53]. Frequent vigorous exercise was associated with 30 % lower risk for ED [25]. Recently, Charansonney et al. [54] suggested that sedentary lifestyle (lack of physical fitness, reduced level of physical activity, and a perpetual level of sedentary behavior) represents independent factors that need be addressed simultaneously when

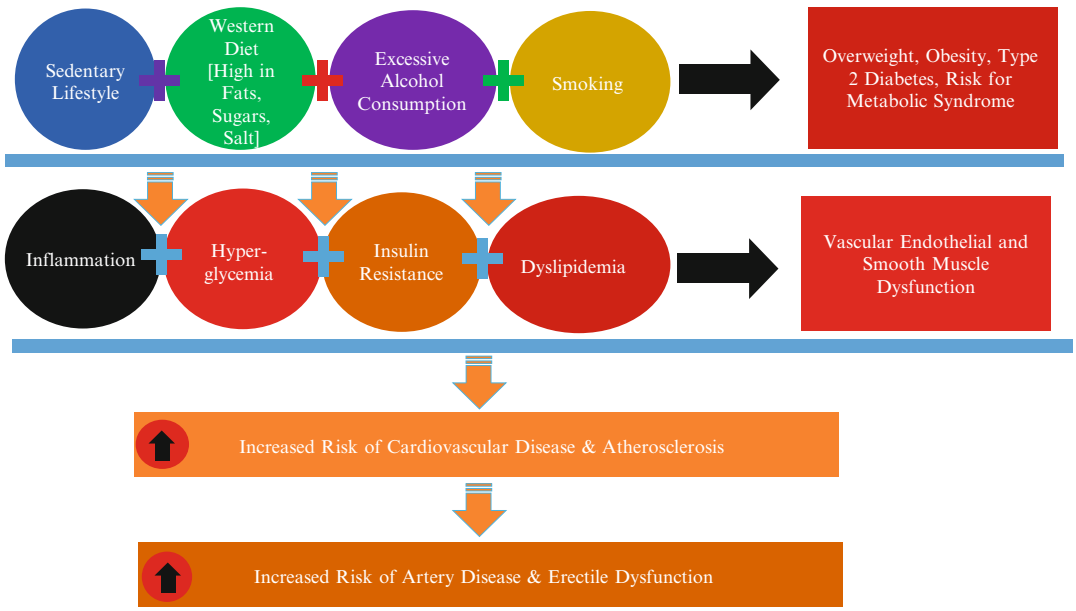

Fig. 8.2 Risk factors associated with erectile dysfunction

Table 8.1 Relationship between obesity and erectile dysfunction

Study	Number of subjects in the study	Major findings	Comments
Feldman et al. [23]	Five hundred thirteen men from MMAS, aged 40–70 years with no ED, diabetes, heart disease, or related medications	Men with BMI ≥28 predicted incident ED. Adjusted 8-year cumulative incidence of ED in overweight/obese men 22 % vs. 13 %	An adjusted odds ratio for overweight/obesity and ED (1.96) was noted suggesting obesity is a risk for ED
Esposito et al. [24]	This study investigated 110 subjects	Reduced BMI was associated with increased IIEF score	The findings suggest a relationship between obesity and ED
Bacon et al. [25]	This epidemiological study involved 31,742 men aged 53–90 years	Obesity is associated with higher risk of ED	The results of this study point to obesity as a risk factor for ED
Blanker et al. [26]	A community-based study of 1688 men aged 50 to 78 years	Obesity is associated with ED	Obesity, is an important correlates of significant ED in the population
Fung et al. [27]	Five hundred seventy men from the Rancho Bernardo Study evaluated 25 years earlier	Obesity is a strong predictor of ED, with age-adjusted BMI significantly higher in men with severe complete ED	The findings suggest that odds ratio for obesity predicting ED = 2.02, which was greater than age (1.12) and hypercholesterolemia (1.76)
Moreira et al. [28]	A population-based sample of 342 men, aged 40–70 years (mean age 49.1)	Obesity is associated with increased prevalence of ED, decreased sexual activity and sexual satisfaction	Age-adjusted odds ratio for moderate or complete ED is 3.0 for obesity, compared to 3.1 for heavy smoking and 12.3 for diabetes
Derby et al. [29]	Analyses included 593 men without erectile dysfunction at baseline	Obesity was associated with ED with baseline obesity predicting a higher risk irrespective of follow-up weight loss	Early adoption of healthy lifestyles may be the best approach to reducing the burden of ED on the health and well-being of older men
Chung et al. [30]	Three hundred and twenty-five consecutive patients with ED were evaluated	There was a statistically significant decrease in the quality of residual erectile function in patients with obesity	Obesity does not seem to be an underlying factor, but does impose a risk to vasculogenic ED by developing chronic vascular disease
Han et al. [31]	Men ($n = 3369$) aged 40–79 years (mean age 60) from European Male Aging Study	Obese men and men with high waist circumference (WC) exhibited more ED than lean men	Both high BMI and high WC are associated with impaired sexual functioning in men
Janiszewski et al. [32]	Men ($n = 3941$) aged 20 years and older (mean age 44.9) were included in the study	Men with ED are more likely to have high BMI, large WC, and low level of physical activity	Obesity, large WC, and low physical activity are associated with ED
Cheng and Ng [33]	Men ($n = 923$) aged 26–70 years were included in the study	The relationship between BMI and ED risk appears to be U-shaped	In physically inactive men a relationship between high BMI and ED was noted
Corona et al. [34]	Men ($n = 3369$) aged 40–79 years (mean 60) from European Male Aging Study were included	ED was identified in 30 % of men, with adjusted odds ratios greater than 1.0. for obese men	The adjusted odds ratios for ED appear similar for obesity, cardiovascular disease, and diabetes
Bajos et al. [35]	Random sample of 4635 men	Obese men are more likely to report ED	Obesity related to sexual dysfunction in men

Table 8.2 Effects of hyperlipidemia and statins treatment on erectile function

Study	Number of subjects in the study	Major findings	Comments
Nikoobakht et al. [36]	One hundred subjects with organic ED, were compared with those in 100 healthy individuals	IIEF score were −0.036 and −0.035, (95 % confidence interval: 0.98–2.5 for cholesterol and 1.13–2.81 for LDL), respectively	High cholesterol and LDL may contribute to ED and this should be considered a risk factor in treatment in prevention of ED
Roumeguere et al. [37]	Two hundred and fifteen subjects had ED and 100 without ED	HDL-C and total cholesterol/HDL-C ratio as significant predictors of ED ($p=0.011$ and 0.000 respectively)	HDL-C and TC/HDL-C ratio are predictors of ED ED might serve as sentinel event for coronary heart disease
Solomon et al. [38]	IIEF scores were measured in 93 men attending cardiovascular risk clinics	After statin therapy, IIEF scores were reduced to 6.5 (range 0–25) ($p<0.001$), and 22 % experienced new onset ED	ED is more likely in patients with severe endothelial dysfunction due to established cardiovascular risk factors including dyslipidemia
Bank et al. [39]	Sixty three men were treated for 3 months with atorvastatin 40 mg ($n=12$), quinapril 10 mg ($n=10$), or placebo ($n=13$)	There was a trend toward a significant improvement in IIEF-5 with atorvastatin. Similarly, quinapril significantly improved the IIEF ED Domain ($p<0.05$)	Treatment with quinapril, in combination with sildenafil, improved ED. Atorvastatin demonstrated a trend toward improved ED in this group
Dadkhah et al. [40]	Men with ED were randomized either to 40 mg atorvastatin daily ($n=66$, group 1) plus sildenafil or matching placebo ($n=65$, group 2) plus sildenafil for 12 weeks	The atorvastatin group had significantly greater improvements in all IIEF-5 questions ($p=0.01$) and GEQ ($p=0.001$ compared to the control group	Patients with moderate and severe ED had better positive response rates to adjunctive atorvastatin than patients with mild to moderate ED
El-Sisi et al. [41]	Sixty patients were randomly divided into three groups: (1) atorvastatin, (2) vitamin E and (3) a control group	Atorvastatin showed a statistically significant increase IIEF-5 score (53.1 %, $p<0.001$) and Rigiscan rigidity parameters ($p<0.01$)	Atorvastatin, but not vitamin E, is a promising drug for sildenafil nonresponders
Gokce et al. [42]	One hundred and twenty subjects with a minimum 3-month history of moderate-to-severe ED were studied	Mean improvement of IIEF score was significantly higher in tadalafil group compared to atorvastatin ($p=0.01$) and control group ($p=0.0001$)	Atorvastatin alone seems to improve EF compared to not using any medication, and this significance is more prominent in patients with supranormal serum lipid levels
Herrmann et al. [43]	Twelve men with a mean domain score of 8.2 ± 6.9 and a mean duration of ED of 3.7 years were enrolled in the study	Improvement with sildenafil in domain score of 7.8 ($p=0.036$); an effect was apparent by 6 weeks. The increase in domain score in placebo patients was not statistically significant	Treatment with atorvastatin improved sexual function and the response to oral sildenafil in men who did not initially respond to treatment with sildenafil

(continued)

Table 8.2 (continued)

Study	Number of subjects in the study	Major findings	Comments
Mastalir et al. [44]	Twenty one subjects received 20 mg simvastatin and twenty received placebo daily for 6 months	After 7 months, all patients on simvastatin group progressed to mild ED, compared with only 83 % in the placebo group	This study does not support the use of simvastatin as erectogenic medication
Trivedi et al. [45]	Men with untreated ED ($n=173$) were randomized to double-blind treatment with 40 mg of simvastatin or placebo once daily for 6 months	No significant difference in erectile function between the simvastatin and placebo groups was noted	Identifying men with ED provides an opportunity to modify future cardiovascular risk and to improve quality of life by treating them with simvastatin
Nurkalem et al. [46]	Ninety consecutive male hypercholesterolemic patients who were otherwise healthy were included into the study prospectively	No statistical differences in mean IIEF score in both groups at the beginning. After 6 months	Rosuvastatin showed no effect on ED while we observed increased ED with atorvastatin. Different statins may exhibit different effects on ED
Gokkaya et al. [47]	Twenty-five patients with a single risk factor dyslipidemia were included in the study	The IIEF score after combined treatment was significantly higher than in the sildenafil and atorvastatin treatment groups	Reducing serum cholesterol levels with atorvastatin could improve erectile function in patients who have only hypercholesterolemia as a risk factor for ED
Saltzman et al. [48]	Nine men with increased cholesterol and organic ED were included in the study	Clinically eight of the nine men had improved erection adequate for penetration during sexual intercourse	EF improves in men with hypercholesterolemia as the only risk factor for ED when treated with atorvastatin

developing a comprehensive plan to manage lifestyle and behaviorial changes. Risk factors associated with ED include sedentary lifestyle and physical inactivity, poor nutritional diets, MetS, excess weight or obesity, cigarette smoking, and excessive alcohol consumption. These risk factors also contribute to endothelial dysfunction and reducing synthesis and release of nitric oxide (NO), thus reducing genital blood flow during sexual stimulation and increasing ED [55]. An association between ED and CVD has been reported in a number of studies. Although the exact link is not fully established, it is believed that the link encompasses a host of pathophysiological mechanisms including chronic inflammation, dyslipidemia, endothelial dysfunction, TD, and atherosclerosis [56, 57]. ED is thought to be an early warning indicator of systemic endothelial dysfunction and CVD risk. Since ED often precedes CVD, clinically ED should serve as an early warning sign for identifying men at higher risk of CVD events [56].

Diabetes contributes to risk of ED via several pathophysiological mechanisms including reduced circulating testosterone (T) levels, peripheral nerve neuropathy, endothelial dysfunction, and impaired smooth muscle contractility [58]. Other mechanisms include reduced nitric oxide synthase (NOS) activity and increased reactive oxygen species (ROS). Insulin resistance (IR), poor glycemic control (increased levels of glucose and glycosylated hemoglobin A1c (HbA1c) and complications of Type 2 diabetes mellitus (T2DM) are thought to link the increased prevalence rates of ED in patients with diabetes [59, 60].

As shown in Table 8.1, obesity is a risk factor for ED [23–35] and weight loss (WL) via lifestyle changes, pharmacotherapy or bariatric surgery has been shown to improve EF. Lifestyle and behavioral changes, resulting in reduced fat mass (FM) and increased lean body mass (LBM), were associated with maintenance of EF [25]. Men with a BMI > 28.7 are at 30 %

higher risk for ED than those with a normal BMI (≤25) [30, 61]. The Massachusetts Male Aging Study (MMAS) and the Rancho Bernardo Study reported that body weight was an independent risk factor for ED [23, 27]. Central adiposity is associated with a state of inflammation and this contributes to endothelial dysfunction [62]. Furthermore, obesity contributes to insulin resistance (IR), MetS, endothelial dysfunction and subclinical inflammation, which in turn contribute to ED [63]. Traish et al. have reviewed the effects of MetS on vascular disease, IR and ED and suggested a common link between vascular disease and ED in men with MetS, T2DM, or CVD [49–51]. Finally, MetS and obesity contribute to hypogonadism. Thus, reduced T levels further contribute to the incidence and pathology of ED [64].

Lifestyle Modification and EF

The effects of lifestyle changes on erectile function are summarized in Table 8.3 [25, 29, 65–74]. A number of studies have demonstrated some improvement in EF with lifestyle changes, albeit modest in nature. Clearly, lifestyle coupled with other interventions should be integrated in the management of ED. Below we summarize the impact of diet, exercise, and pharmacotherapy on ED.

Diet

The diet of Western culture has significant implications on health. The impact of diet on EF is complex and not easily evaluated. Limited data are

Table 8.3 Relationship between changes in lifestyle and ED

Study	Number of subjects	Major findings
Kalka et al. [65]	150 men being treated for ischemic heart disease randomized to undergo cardiac rehabilitation for 6 months	IIEF score significantly increased in men undergoing cardiac rehabilitation exercise program, and surrogate measures of cardiovascular risk factors decreased significantly
Khoo, et al. [66]	90 men w/BMI > 27.5 randomized to high or low volume exercise	Activity levels increased in both groups, and IIEF score was significantly increased in both groups. Serum T levels increased in the high volume exercise group
Hsiao et al. [67]	Observational study of 78 men examining association of activity level w/ED	Sedentary men showed significantly higher rates of ED compared with active men. They also had lower scores on measures of sexual function and satisfaction
Bacon et al. [25]	Cross-sectional analysis of 31,742 men over age 50	Physical activity associated with lower risk of ED. Obesity, smoking, and TV viewing time were also associated with increased risk of ED
White et al. [68]	78 sedentary men undertook 60 min of moderate exercise 3.5 times a week were compared to 17 men who walked 60 min four times a week	Men who undertook significant exercise experienced lower rates of sexual problems than controls by self-report diaries. Increasing fitness was associated with increasing sexual function
Hannan et al. [69]	A review of current literature on ED and CVD risk factors	Physical inactivity decreases erectile function. Exercise interventions are able to reverse some erectile dysfunction
Ettala et al. [70]	Cross-sectional analysis of 1000 men with cardiovascular risk factors	Age (OR 9.16 [5.00–16.79]), smoking (OR 1.41 [1.04–1.91]), and high intensity physical activity (OR 0.5 [0.29–0.86]) were associated with ED by IIEF score
Derby et al. [29]	A prospective cohort of 593 men aged 40–70 without ED at baseline were followed (mean 8.8 years) by survey for ED incidence	Obesity and low physical activity levels were associated with increased incidence of ED

(continued)

Table 8.3 (continued)

Study	Number of subjects	Major findings
Johannes et al. [71]	1709 men form the Massachusetts Male Aging Study were surveyed over a 6–10-year period	Incidence of ED increased with each decade of age, and diabetes (RR 1.83), treated CVD (RR 1.96), and treated hypertension (RR 1.52) were correlated with increased incidence of ED
Cheng et al. [72]	Meta-analysis of 11 studies assessing the link between physical activity and ED	Pooled, adjusted odds ratios showed an increased risk of ED among low physical activity men (OR 0.53). Furthermore, high and moderate intensity exercise led to a decreased incidence of ED (OR 0.62)
Esposito et al. [24]	110 men were randomized to receive intensive education on achieving 10 % weight loss through caloric restriction and exercise or generalized information on healthy behaviors	Men in the intervention group lost significantly more weight than the controls and demonstrated a significantly increased IIEF score (13.9–17 vs. 13.5–13.6)
Lamina et al. [73]	22 men with ED and hypertension underwent an exercise program (45-60 min/day) for 8 weeks and were compared to sedentary, age-matched controls	Exercise training in hypertensive men led to a significantly increased IIEF score compared to controls (15.14 vs. 8.95)
Korhonen et al. [74]	924 men at risk for CVD or diabetes were assessed for IIEF scores and hypertension	In an adjusted model, hypertension and ED were not significantly associated. However, depressive symptoms modified this association, with the presence of these symptoms increasing the risk of ED in hypertensive men more than their hypertensive counterparts (OR 2.44 vs. 7.62)

available suggesting that dietary changes may improve EF. The Western diet tends to be high in saturated fats, sugars, and sodium, while simultaneously being low in fiber and protein. This type of diet promotes hypercholesterolemia, hyperglycemia, increased BMI and adiposity, and hypertension, among others [75]. The Western diet is thought to be significantly associated with ED development [55]. Several studies suggested that modification of diet can improve symptoms of existing ED and prevent ED development [76, 77].

The likely mechanism by which diet may influence ED is thought to be related to increased hypercholesterolemia [78]. Hypercholesterolemia upregulates activity of the enzyme arginase, which competes with NOS for the substrate L-arginine. Upregulation of arginase attenuates NO synthesis, and the ability to achieve and maintain erection is impaired. Furthermore, dyslipidemia contributes to endothelial dysfunction and reduction of endothelial NOS activity. In fact, rats fed a Western diet were shown to have a significant decline in EF [79, 80]. Hypercholesterolemia also results in decreasing activity of vascular endothelial growth factor (VEGF) and other vasculogenic factors involved in vascular endothelial maintenance of function [81]. Findings in animals fed high-fat diets include elevated oxidized LDL and reduced eNOS activity, coincident with an increased risk for coronary artery disease and endothelial damage [79, 80, 82]. Moreover, a low fat and low sugar diet has been shown to reduce systemic inflammatory markers [55]. This mechanism is thought to contribute to improved endothelial function, leading to increased eNOS activity and improved NO production.

Reduction of hypercholesterolemia and achieving glycemic control are proposed therapeutic strategies to prevent ED by reducing inflammation, restoring endothelial function, and increasing the availability of L-arginine [83]. Relatively large amounts of L-arginine are found in legumes and whole grains—since this is the

primary precursor to NO, it stands to reason that increased consumption of these foods may improve maintenance of EF [84, 85]. This is part of the reason why the Mediterranean diet is the most investigated dietary intervention for ED [69, 86–88].

Other diets and nutritional supplements have been investigated within this realm, but most have failed to show positive results or have not been rigorously investigated [84, 85]. For this reason, transition from the Western diet to Mediterranean diet should be considered in men suffering from ED. Esposito and colleagues [86, 87] have described a small but significant section of research demonstrating benefit to the Mediterranean diet in ameliorating ED. Esposito et al. [86] reported on the effects of a Mediterranean diet (fruits, vegetables, grains, and olive oil) on EF in 65 men with metabolic syndrome and ED. In this study, 35 men were placed on the Mediterranean diet and 30 men maintained on a normal diet served as control. After 2 years of follow-up, an improvement in EF (IIEF-5 > 22) in 13 men in the intervention group and only two in the control group was reported [86]. In men with T2DM, who adhered to the Mediterranean diet showed lowest presence of ED. Also, Mediterranean diet was more effective than the control diet in ameliorating ED or restoring EF in men with obesity and metabolic syndrome [87, 89–91]. In fact, fruit and vegetable intake alone has been negatively correlated with ED rates in men [92]. Additionally, low fat diets, along with low-fat/high-protein diets, are shown to reduced symptoms of ED [93, 94]. Overall, dietary changes have been shown to have a positive impact on EF [86, 87, 89–91]. The most striking element of this intervention is its positive impact on multiple CVD risk factors that are commonly linked to ED. The low fat diet coupled with high-protein diet is shown in clinical trials to reduce waist-hip ratio (WHR), serum lipid levels, and systemic inflammatory markers, with the impact on these surrogates increasing with increased adherence [88, 95].

The Western diet contributes significantly to negative health outcomes including ED. Promoting healthier eating, including reduction of saturated fats and sugars, contributes to improving EF in men suffering from clinical symptoms. It is likely that most men would benefit from caloric restriction and increased physical activity, and therefore dietary changes should be considered as an adjunct to exercise and WL programs, in conjunction with standard pharmacotherapeutic interventions. It is possible that ED could be a sentinel event for CAD [79, 96]. Although this is still somewhat controversial, improved diet is widely considered to have a beneficial impact on cardiovascular health. In combination with the evidence favoring improved diet in ameliorating ED, the modification of this risk factor should be encouraged in all patients. There have been few clinical trials examining other diets such as the Mediterranean diet, but the reported results are encouraging and support the use of this diet in ameliorating ED. Additionally, some of the individual aspects of the Western diet are supported as an independent element by research cited above [92–94].

In summary, while the evidence for dietary intervention in improving EF and reducing ED is limited, we feel that both common sense and the presented evidence support a role for dietary changes in the non-pharmacological treatment of ED. A focus on reduction in saturated fat and cholesterol content, increased fruit and vegetable consumption, and moderately increased protein should serve the purposes of most interventions. The Mediterranean diet could easily be used to guide these interventions.

Exercise

Cardiovascular health is inextricably linked to overall health, and ED is no exception. Many cardiovascular (CVD) risk factors are therefore significantly associated with ED in men with a range of health conditions, including both patients with and without clinical CVD [52, 70, 84, 85]. Since erectile physiology shares many common risk factors with CVD, this prompted a host of studies to determine if physical activity contributes to prevention of ED and/or produce significant clinical improvement in EF [83].

Both WL and increased physical activity are correlated with increased IIEF scores [67], while sedentary lifestyle is associated with decreased IIEF scores [29]. Therefore, exercise is examined as a potential primary intervention for men suffering from ED.

Risk factors such as obesity (Table 8.1) [23–35], increased BMI, increased blood pressure (BP), increased hypercholesterolemia (Table 8.2) [36–48], and reduced physical activity are linked with incidence and prevalence of ED [67, 69, 70]. All of these risk factors contribute to increased inflammatory cytokines, such as IL-6 and TNF-a, which are implicated in IR. Therefore, these risk factors perturb vascular endothelial structure and function and result in reduced NO production and attenuate NO signaling. Furthermore, upregulation of arginase by hypercholesterolemia further contributes to reduction in NO by limiting the availability of L-arginine as a substrate for NOS [76].

Extended periods of bed-rest, as an extreme model of a sedentary lifestyle, are shown to modify blood vessel structure [97, 98]. Hypertension also modulates the function of the vascular endothelium, further contributing to the structural and functional changes associated with CVD risk described above [69]. Moreover, it is likely that sedentary lifestyle is associated with a state of hypogonadism (TD) and reduced total testosterone (TT) levels and contributing to poor cardiovascular health and ED [99–102]. In the model of bed-rest, however, an exercise regimen was insufficient to restore the structural and biochemical changes already produced by the sedentary period. Therefore, cases of ED induced by severe inactivity may not benefit from exercise intervention alone. Finally, a direct link between the development of atherosclerosis and ED has been proposed but it is exceedingly difficult to assess the link between these variables independently in the models discussed [103]. The goal of cardiovascular and exercise interventions is primarily to improve the endothelial function, which has been dysregulated by an inflammatory state. Exercise is postulated to act on the endothelium by reducing inflammatory factors, reducing blood pressure, and restoring normal lipid profiles from the acquired state of dyslipidemia. Furthermore, exercise is known to reduce BP, which modulates the function of the vascular endothelium in a manner beneficial to EF.

In a preclinical animal model of exercise intervention, it was shown that exercise duration and intensity were positively correlated with EF [79, 80]. In this model, ED was induced by a western diet known to contribute to the risk factors of ED. The possibility of altering this risk factor through exercise was experimentally demonstrated in this preclinical animal model study [79, 80].

Several studies showed that significant changes in EF are induced by exercise. In the Massachusetts Male Aging Study (MMAS) it was reported that a 30 % lower risk in developing ED was observed in physically active men compared to sedentary men and increased physical activity was independently associated with a reduced risk of incident ED [29, 71]. Men who remained sedentary exhibited the highest risk of developing ED and the lowest risk was noted among those who remained active or initiated physical activity during this time period [29, 71]. A meta-analysis of 11 studies suggested that physical activity exerts a protective effect on maintaining EF, and ED was negatively correlated with physical activity [72]. Esposito reported that EF improved significantly in men placed on regiment of diet and exercise (IIEF-EF score 13.9–17.0) but did not change in the control group (mean score 13.5–13.6) [24, 91]. Lamina et al. reported a significant benefit of the exercise-training program on improving EF in hypertensive men with ED after 8 weeks [73].

In a meta-analysis Gupta et al. [104] showed a significant benefit to cardiovascular intervention as a treatment for ED. Treatments aimed at reducing CVD risk factors among patients with ED include exercise programs, dietary changes, WL, and statin therapy. All of these interventions were shown to improve the IIEF score of patients concomitant with a reduction of CVD risk factors [48]. Most importantly, these interventions were effective in men nonresponsive to PDE-5 inhibitors therapy of ED. This suggests that the benefits of cardiovascular interventions may go beyond

simply improving endothelial function and increasing NO production.

Simply, increasing exercise levels in men with symptomatic ED may restore their EF [68]. White and colleagues assessed the effect of exercise alone on sexual function in men [68] and reported that a 9-month exercise intervention (60 min/day, ~3.5 days/week at 75–80% maximum aerobic capacity) significantly enhanced the frequency of intercourse, orgasms, and maintained erections as recorded in sexuality diaries of the exercising group compared with the control group that were prescribed a low-intensity walking program. A comprehensive literature review by Hannan et al. [69] further supported the data reported by White et al. [86]. In fact, increasing duration and intensity of exercise further improves EF with a concomitant reduction in CVD risk factors including reduced BMI and adiposity. Intensive cardiac rehabilitation programs significantly improve the IIEF scores of men with ED [69]. This holds true among various risk stratifications including otherwise healthy men with severe ED, men with age-related ED, obese men, and men treated for ischemic heart disease [65, 66, 97, 98]. These interventions show a benefit in CVD risk factors including reduced BMI and low density lipoprotein (LDL) and increased levels of high density lipoprotein (HDL).

The interactions between cardiovascular health and ED are complex and involve a multitude of factors. However, two major aspects are clear: the proactive treatment of CVD risk factors in men with ED is beneficial, and increasing physical activity levels is effective for improving sexual function [83]. There is some controversy over the association of ED with hypertension [74]. While targeting blood pressure alone may not be fully effective, the data strongly suggest that exercise has a significant benefit on EF independent of blood pressure, and therefore a reduction in hypertension can be considered a fringe benefit to this intervention. Because exercise is associated with increased IIEF scores in men resistant to PDE-5 inhibitors, increasing activity levels should be considered as a primary intervention for men with ED. The benefits of exercise in overall health are innumerable, and therefore should be encouraged in all eligible men complaining of ED.

In summary, humans are not programmed to be inactive [105]. The combination of sedentary lifestyle and food availability disrupts metabolic processes leading to excessive energy storage, dyslipidemia and insulin resistance. As a consequence, the prevalence of T2DM, obesity and the MetS has increased significantly over the last 30 years. Physical inactivity leads to the accumulation of visceral fat and consequently the activation of the oxidative stress/inflammation cascade, which promotes the development of atherosclerosis. Exercise promotes atheroprotection likely by reducing or preventing oxidative stress and inflammation through at least two distinct pathways. Exercise, through laminar shear stress activation, downregulates endothelial angiotensin II type 1 receptor expression, leading to decreases in NADPH oxidase activity and superoxide anion production, which in turn decreases ROS (reactive oxygen species) generation, and preserves endothelial NO bioavailability and its protective antiatherogenic effects. Contracting skeletal muscle releases anti-inflammatory cytokines, which inhibits TNF-α (tumour necrosis factor-α) production in adipose tissue and macrophages. The downregulation of TNF-α induced by skeletal muscle-derived ctyokines may also participate in mediating the atheroprotective effect of physical activity [105].

As discussed by several investigators [106–108], exercise exerts direct effects on the vascular wall of arteries, a concept recently referred to as vascular conditioning. The vascular effects of exercise may include structural (angiogenesis and remodeling) and functional adaptations, the latter involving phenotypic alterations of vascular smooth muscle and endothelial cells. The effects of exercise on the endothelium may explain, at least in part, the well-established association between physical activity and reduced cardiovascular events and mortality [109]. In addition, the immune system and inflammation play a central role in the development of numerous chronic metabolic diseases including insulin resistance (IR), type 2 diabetes (T2DM), atherosclerosis, nonalcoholic fatty liver disease, and

specific types of cancer [110]. Exercise is anti-inflammatory in nature. The cytokine profile induced by exercise is classically anti-inflammatory, comprising marked increases in the levels of several potent anti-inflammatory cytokines such as IL-10, IL-1 receptor antagonist (IL-1ra), and IL-6. Although exercise can be pro-inflammatory and has, in some instances, been associated with increased production of pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1beta (IL-1β), and C-reactive protein, this is typically only the case after extreme forms of exercise such as marathon running or Ironman triathlon, which are associated with muscle damage and even systemic endotoxemia. The adipose tissue immune cell profile changes dramatically in the transition from the lean to the obese state. Numerous immune cell types have been shown to contribute to adipose tissue inflammation and systemic IR in the obese state or, by contrast, contribute to the maintenance of insulin sensitivity in the lean, healthy state [110].

Weight Loss

Weight Loss with Diet and Exercise

Obesity is a significant independent risk factor for development of ED [23–35, 90]. The relationship between WL and ED is summarized in Table 8.4 [24, 75, 77, 95, 111–119]. Decreasing the burden of increased fat mass (FM) and body mass index (BMI) is important for overall health and also represents a potential therapeutic target in the management of ED. There is a significant burden of ED among overweight men, with an increased prevalence of ED in men with increased BMI and/or increased abdominal FM [29, 75, 95, 111]. Men with BMI of 25–30 kg/m^2 had increased risk of ED, being as high as 30 % [90]. This risk increases even higher in men with a BMI > 30 kg/m^2 [120]. Strikingly, weight not only predicts ED incidence but also the chances of remission [111]. It has further been shown that bariatric surgery-induced WL increased EF, as assessed by IIEF-5 questionnaire. This also resulted in increased total testosterone (TT) and free (FT) levels. It was suggested that the hormonal changes may have contributed to the improvement in EF. Therefore, while the modification of lifestyle alone had had an effect on BMI, hormonal changes were integral to the significant improvement observed [112].

Increased BMI is associated with increased inflammatory cytokines such as TNF-α, IL-6, and C-reactive protein (CRP) [76]. Increased weight and FM are also associated with increased IR and reduced insulin sensitivity and reduced NO production and function [121–123]. The contribution to the pathophysiology of ED by these inflammatory factors is most likely through a generalized endothelium dysfunction, induced by the inflammatory state [124, 125]. Finally, obese men are prone to hypogonadism [126, 127]. The potential mechanism by which WL would reverse ED is via improvements in endothelial function and NO production and improvement in insulin sensitivity. Also, increased TT levels via WL may act to attenuate the inflammatory state experienced by obese men [127].

It is difficult to clinically separate the effects of WL and increased exercise on ED due to their covariation with one another. Maio and colleagues [77] conducted a study in animals to assess the effects of a calorie restricted diet on the development of ED. In animals that were fed a restricted calorie diet there was no ED, whereas animals fed high fat diet ad libitum demonstrated increased rates of ED. Further, a study conducted by Reis and colleagues [112] demonstrated the effects of surgical WL on EF and other associated factors. When morbidly obese men were subjected to an intensive WL regimen, they showed a significantly reduced BMI compared with their control counterparts, but were equivalent on international index of erectile function (IIEF) and hormonal measures. However, when these men underwent gastric bypass surgeries, WL correlated with improved EF and measures of circulating TT. These studies support the notion that WL intervention could significantly affect ED outcomes. Therefore, irrespective of the potential mechanisms of WL, improvement in EF is noted with WL (Table 8.4) [24, 75, 77, 95, 111–119].

WL has been shown to improve EF [24, 62, 91]. Regular follow-up and counseling are effec-

Table 8.4 Relationship between weight Loss and ED

Study	Number of subjects	Major findings
Capogrosso et al. [75]	A cross section of 439 men was analyzed by age group (±40 years) for socio-demographic and clinical differences relating to ED	Approximately 26 % of incident ED cases were found in men under 40 years. Smoking and drug use was more frequent among younger patients, while BMI, hypertension, and hypercholesterolemia were more frequent in older ED patients
Martin et al. [111]	An observational study of 810 men over a 5-year period	Predictors of incident ED in the follow-up period included increasing age, low income, increased abdominal fat mass, depression, and diabetes
Giugliano et al. [95]	A cross section of 555 men with type 2 diabetes was analyzed for factors associated with ED	Increasing age, HbA1c, dyslipidemia, metabolic syndrome, and BMI were associated with ED
Maio et al. [77]	A study in rats was conducted to assess the impact of mild and moderate caloric restriction on erectile function	While body weight was negatively correlated with erectile function, visceral adipose tissue (VAT) was the strongest predictor of decreased erectile function ($R^2 = 0.74$). Caloric restriction successfully maintained erectile function and decreased VAT
Reis et al. [112]	An RCT was conducted comparing 4 weeks of lifestyle modification followed by gastric bypass surgery to simple follow-up alone in 20 morbidly obese men	Lifestyle intervention achieved a significant BMI reduction compared to control, and there was a further BMI reduction following surgery. IIEF score, FSH, and TT increased significantly in the intervention group compared to control, only following surgery
Kun et al. [113]	A retrospective cohort assessed 39 obese men with ED undergoing gastric bypass surgery	IIEF score was significantly increased following surgery. Interestingly, decreased BMI was not associated with increased IIEF
Mora et al. [114]	A case series of 39 obese men undergoing bariatric surgery	Bariatric surgery was associated with significantly reduced BMI, increased IIEF score, and increased TT. Interestingly, the improvements seen following surgery were predicted by both the change in BMI and the baseline IIEF score
Rosenblatt et al. [115]	23 obese patients, matched with 14 controls, underwent bariatric surgery	At long-term follow-up, there was significant weight loss, increased TT, and decreased erectile dysfunction compared to controls
Wing et al. [116]	Obese type 2 diabetics in the Look AHEAD trial completed IIEF questionnaires at baseline ($n = 372$) and 1-year follow-up ($n = 306$) of a weight loss intervention	Compared to baseline, participants at follow-up had lost significantly more weight, showed increased fitness, and increased erectile function
Dallal et al. [117]	97 obese men underwent gastric bypass surgery matched to reference controls	In an average 19 months follow-up, men who underwent surgery showed a significant improvement in sexual function on the Male Brief Sexual Function Inventory (BSFI)
Esposito et al. [24]	110 men were randomized to receive intensive education on achieving 10 % weight loss through caloric restriction and exercise or generalized information on healthy behaviors	Men in the intervention group lost significantly more weight than the controls and demonstrated a significantly increased IIEF score (13.9–17 vs. 13.5–13.6)

(continued)

Table 8.4 (continued)

Study	Number of subjects	Major findings
Collins et al. [118]	145 obese men were randomized to receive intensive weight-loss advice via the Internet or control	Men who participated in the weight-loss program demonstrated significantly increased IIEF scores as compared to controls
Esposito et al. [119]	209 men were randomized to receive either intensive advice on weight-loss, exercise, and healthy lifestyle choices or general advice on weight-loss	Men in the intervention group demonstrated significantly increased IIEF scores. When men were assigned a "success score" based on how many goals they met, this score was positively correlated with increased IIEF score

tive behavioral methods for promoting WL, and several studies in this realm reported data on EF. The SHED-IT trial tested gender specific WL guidance, and demonstrated a significant improvement in EF at 6 month follow-up in the intervention group [128]. Esposito and colleagues [119] investigated a specific program of increased activity, caloric restriction, and dietary changes in men with, or at high risk for ED. With a goal of 5 % weight reduction they demonstrated that men partaking in this program had significantly lower rates of ED compared to controls, and reversal of ED symptoms in some patients.

T2DM is not only correlated with increased weight, but also ED. WL interventions in the PULSE trial [129] and the Look AHEAD trial [116] assessed EF in their participants. Both studies consist of education, caloric restriction, and increased exercise. Data from Wing and colleagues [116] show that EF in men from the intervention group improved significantly with a concomitant WL, lower BP and reduction in HbA1c at 1-year follow-up. The PULSE trial has not yet released data, but because the focus is on reducing the costs associated with significant weight-loss the results promise to be exciting.

The deliberate action to produce WL in men suffering from ED is an important treatment strategy. While increased exercise is important first step, caloric restriction must also be implemented to achieve the desired WL which is significant enough to impact EF [130]. It is known that weight regain is a significant problem in most WL strategies. It is likely that increasing weight following intervention could reverse the positive effects of WL on EF, but the data on this topic remain in hot debate. The physician's biggest challenge may lie in WL maintenance, and therefore special efforts should be made to ensure this maintenance in patients who undertake such interventions. Strategies for WL in conjunction with lifestyle changes including pharmacotherapy and bariatric surgery are discussed below.

Weight Loss via Pharmacotherapy

Obesity is a chronic disease, necessitating medical intervention. For example, treatment with the drug "Liraglutide" coupled with a diet and exercise was recently introduced as a treatment for obesity. This approach resulted in sustained and significant WL and reduced CVD risk in obese nondiabetic adults [131]. Furthermore, this treatment resulted in reduction in systolic blood pressure, fasting blood glucose, HbA_{1c} and C-reactive protein concentrations. One key concern regarding pharmacological therapy of obesity and WL is the potential serious adverse side effects and safety concerns, which in many cases have contributed to the withdrawal of a number of drugs that have been previously approved and marketed for treatment of obesity [132]. In a review of 20 studies with a total of 27 intervention arms and 3017 participants, antiobesity drugs, meal replacements, and high-protein diets were associated with improved WL maintenance, but no significant improvements were noted with dietary supplements and exercise alone [133]. It appears that long-term therapy of obesity with pharmacotherapeutic agents offers modest yet variable benefits in most patients [134]. Another concern

is the adherence to therapy. In 2-year trials of liraglutide, approximately 50% of patients did not complete the studies [131, 135].

Weight Loss via Bariatric Surgery

Bariatric surgery results in a substantial and sustained WL and ameliorates several obesity-related comorbidities [136]. In addition, one of the noted benefits of this approach is improvements in the CVD risk profile, such as MetS; a lower risk of ischemic heart disease and mortality. Bariatric surgery increases levels of total T and free T, suggesting that weight reduction via bariatric surgery is associated with normalization of hormonal profiles in obese men [137]. Bariatric surgery increased EF, as assessed by IIEF-5 questionnaire. This was attributed in part to the restoration of the hormonal milieu. It should be emphasized that only carefully selected patients can be subjected to bariatric surgery because of inherent risks and complications. It should be recognized that patients who undergo bariatric surgery must be followed up very closely and carefully. This surgical approach is often associated with medical complications requiring long term monitoring. Most patients will require additional plastic surgery to provide relief from excessive skin tissue. Finally, this approach is costly and may not be affordable for many patients, in light of the potential new additional complications.

Weight Loss via T therapy

T therapy in men with TD improves body composition, with concomitant reduction in FM and increased lean body mass (LBM) [reviewed in ref. [127] and produces significant weight loss (WL), waist circumference (WC), and BMI (Fig. 8.3) [138–144]. More importantly, long-term studies in obese men or men with MetS, T therapy resulted in significant WL, reduction in WC, BMI, HbA_{1c}, insulin resistance (HOMA-IR), total cholesterol, LDL cholesterol, triglycerides, hsCRP, systolic and diastolic blood pressure, and an increase in HDL [142, 144].

Long-term T therapy in men with TD produced significant reduction in total cholesterol, low density lipoprotein-cholesterol (LDL) cholesterol, triglycerides, and increased HDL (Fig. 8.4) [138–145]. Furthermore, T therapy reduced both systolic and diastolic blood pressures (Fig. 8.5) [138–145] and reduced levels of HbA1c (Fig. 8.6) [138–145] and also reduced hs-CRP (Fig. 8.7) [138–145]. Long-term T therapy has been shown to improve EF as assessed by IIEF-5 score in several studies [140, 143, 146, 147]. We suggest that T therapy represents a novel pharmacotherapeutic approach in the treatment of obesity and MetS. We believe that T therapy reduces inflammation, improves EF and increases vigor and reduces fatigue. An improved quality of life can therefore be expected in these men concomitant with appropriate changes in lifestyle and physical activity levels. In summary, long-term T therapy in men with TD improves body composition and quality of life in obese men with TD. Furthermore, this form of therapy ameliorates MetS components and appears to be effective and useful in the management of WL and has been shown to improve erectile function [143, 146, 147].

Smoking

Because smoking affects vascular function, it is believed that smoking is a risk factor for ED. Some studies did not find a significant link between smoking and ED, and therefore this topic remains controversial [23, 148–153]. However, a host of studies presented data to suggest that smoking contributes to the pathophysiology of ED (Table 8.5) [55, 148, 154, 155]. A comprehensive literature review suggested deleterious effect of smoking on erectile physiology [156]. The authors' findings suggested that smokers were more likely to experience higher incidence of ED when compared with nonsmokers. These findings are supported by the work of Feldman et al. [23] who reported that smokers were more likely to suffer from ED than nonsmokers (24% vs. 14%). More recent studies by Kupelian et al. [149] in The Boston Area Community Heath survey found an association between smoking and ED. The authors noted that a significant trend of increased risk of developing ED with cumulative

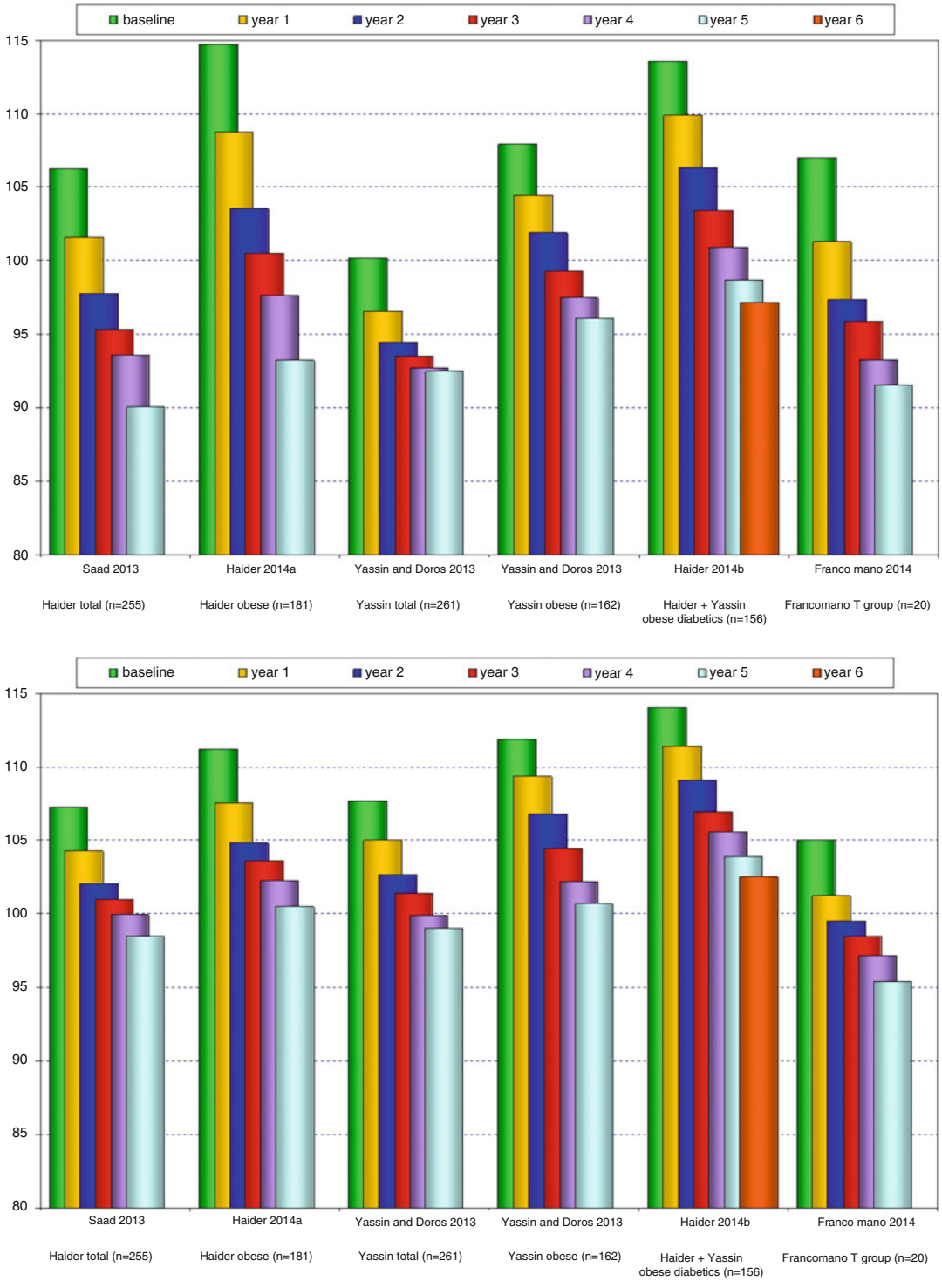

Fig. 8.3 Effects of long-term T therapy on weight loss, waist circumference and body mass index in men with testosterone deficiency. Long-term testosterone therapy in men with TD produced marked and sustained WL (*upper panel*), significant reduction in WC (*middle panel*) and BMI (*lower panel*). The data were reported [138–144]

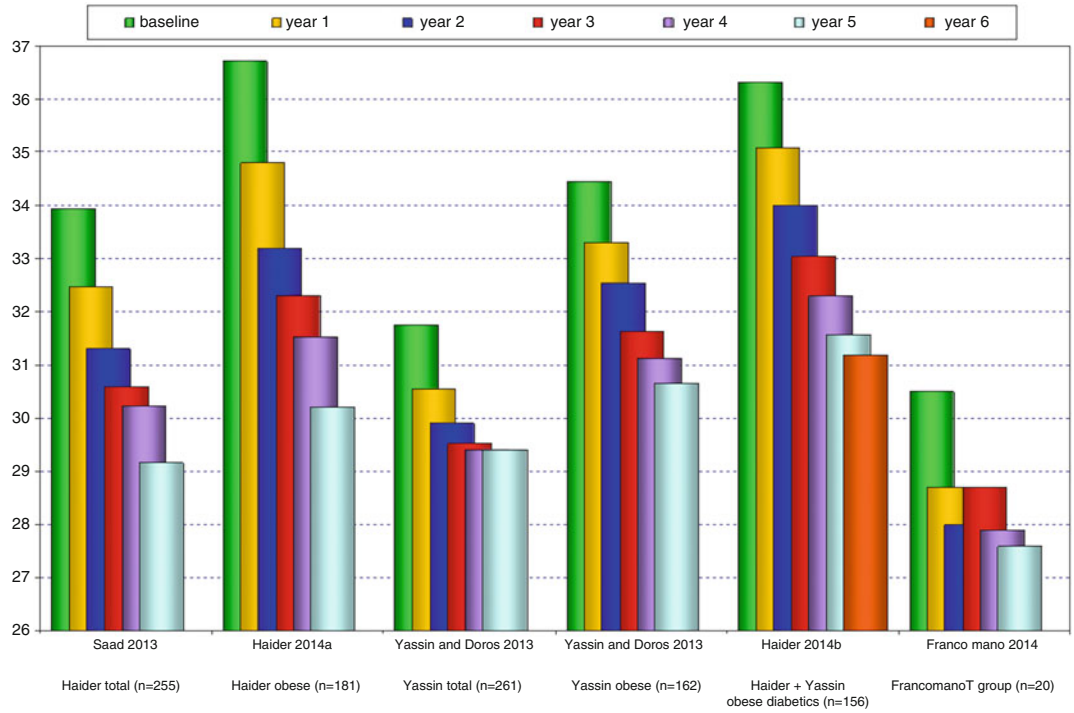

Fig. 8.3 (continued)

pack years of smoking. In men who quit smoking an improvement in EF was noted, albeit small [150]. Further, the authors reported that severity of ED was significantly correlated with the amount of exposure to smoking.

It is proposed that cigarette smoking disrupts normal EF through two primary mechanisms—endothelial damage and ROS production. Both cigarette smoke and ROS have been shown to interrupt the activity of NOS in the endothelium, and inhibiting the binding of NO to guanylyl cyclase [157]. Smoking cessation can reverse the changes caused by ROS in the endothelium and cause significant vasoconstriction [76, 158]. For these reasons, cessation of cigarette smoking could be an appropriate target for treatment in men who present with symptoms of ED, while currently smoking. This presumption is partially supported by an observation that current smokers have lower rates of remission from ED than those who have quit [111].

Few studies have examined the effect of smoking cessation on ED. A prospective study published in 2004 showed that among smokers with clinical ED, 25 % showed improvement in symptoms following successful smoking cessation, compared with only 2.5 % of those who did not quit [150]. In a study conducted by Chan and colleagues [151], 719 smokers were divided among groups to receive nicotine replacement therapy (NRT), counseling, or simple advice on smoking cessation, while their EF was assessed by IIEF at 6 months. Approximately, 55 % of men in this study who successfully ceased smoking demonstrated an improvement in EF compared to only 28 % of those who quit unsuccessfully. Finally, Harte and colleagues [152] assessed the impact of smoking cessation on erectile function. It was found that physiological indicators of EF improved significantly among men who successfully quit, and a faster increase in sexual satisfaction among those men.

The interrelationship of smoking with ED remains controversial. However, we believe that the evidence supports not only a link between smoking and ED but that smoking cessation is a

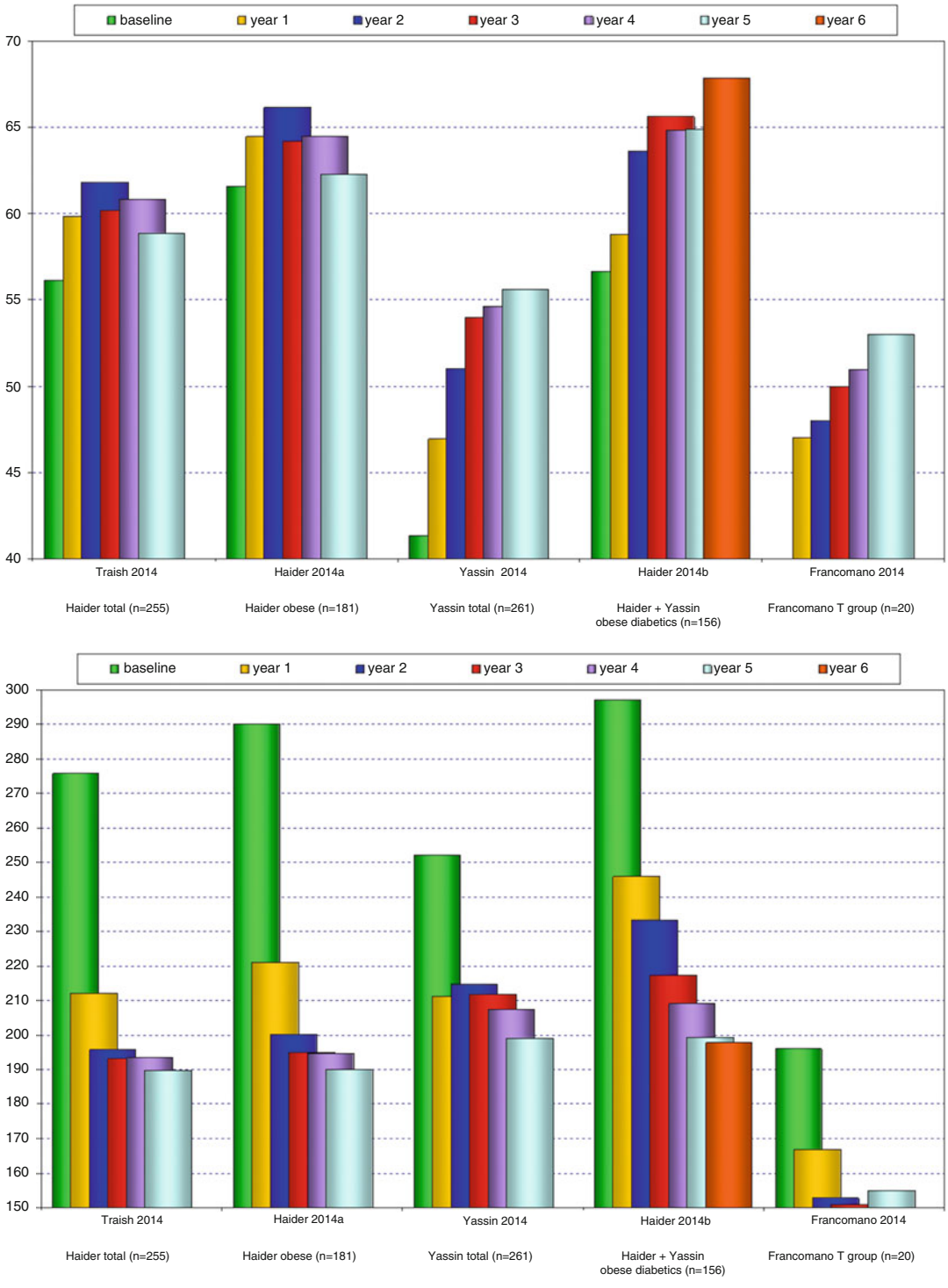

Fig. 8.4 Effects of long-term T therapy on lipid profiles in men with testosterone deficiency. Long-term testosterone therapy in men with TD produced marked and sustained reduction in total cholesterol (upper panel), LDL cholesterol (second panel), and triglycerides (third panel) and increased HDL cholesterol (lower panel). The data have been reported previously [138–144]

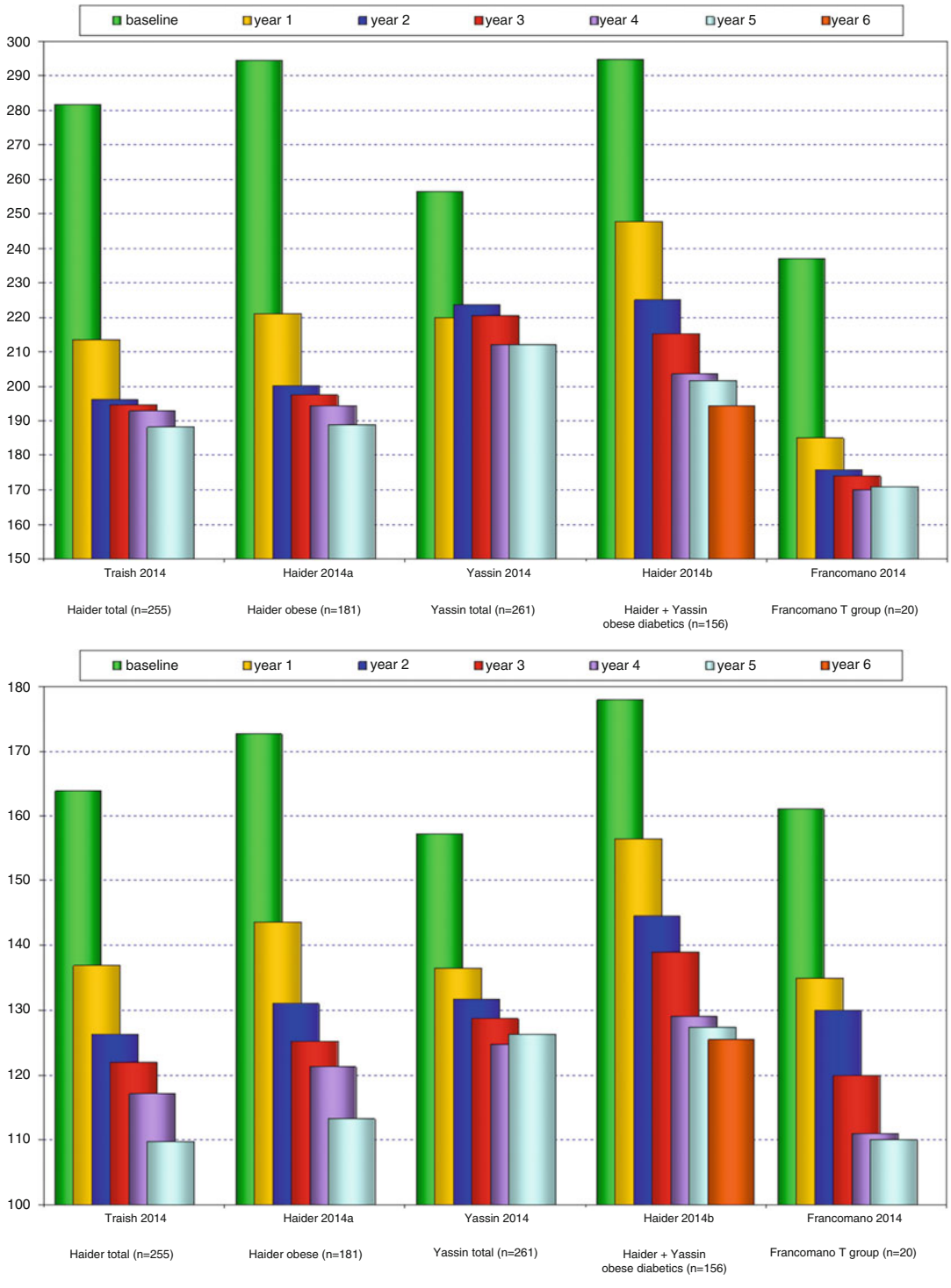

Fig. 8.4 (continued)

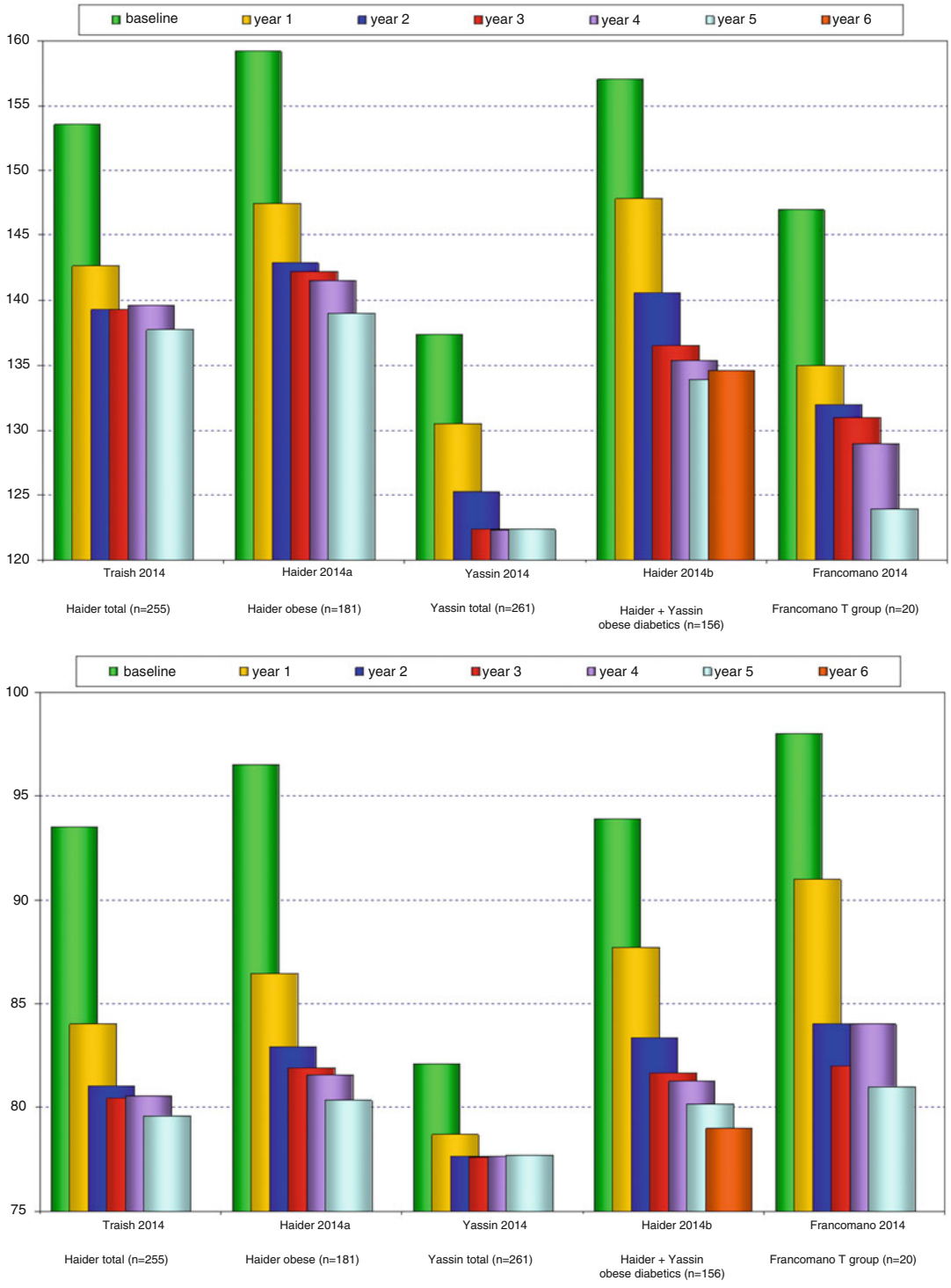

Fig. 8.5 Effects of long-term T therapy on systolic and diastolic blood pressure in men with testosterone deficiency. Long-term testosterone therapy in men with TD produced significant reduction in systolic (*upper panel*) and diastolic blood pressure (*lower panel*). The data have been reported previously [138–144]

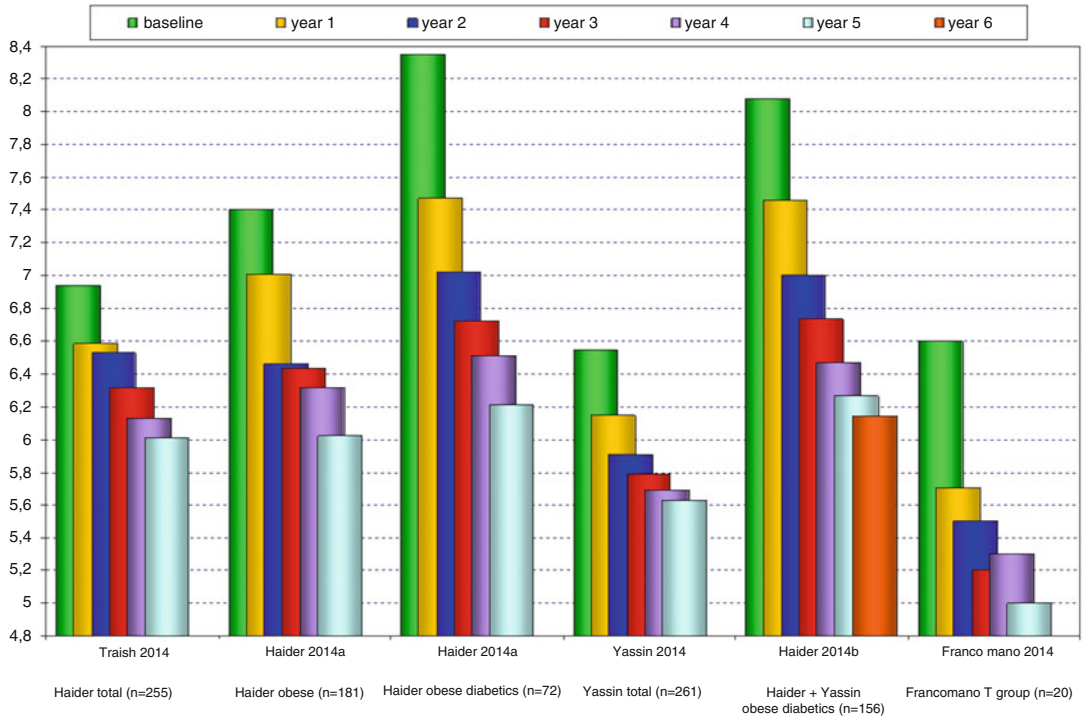

Fig. 8.6 Effects of long-term T therapy on systolic and diastolic blood pressure in men with testosterone deficiency. Long-term testosterone therapy in men with TD produced significant reduction in glycated Hemoglobin (HbA_{1c}). The data have been reported previously [138–144]

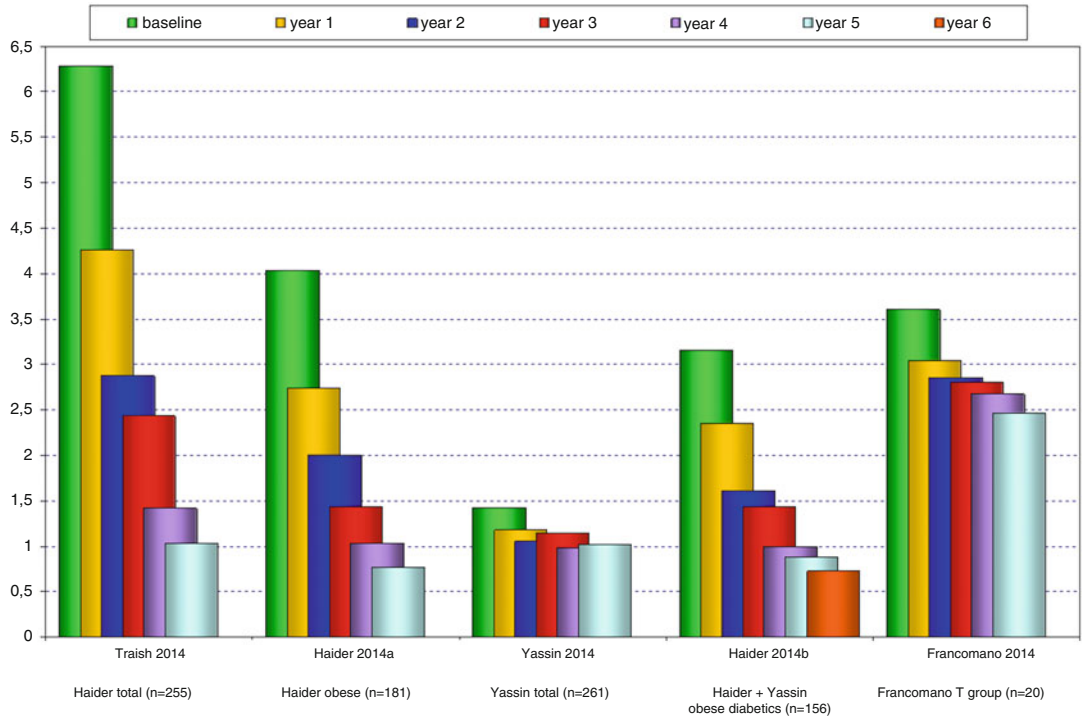

Fig. 8.7 Effects of long-term T therapy on C-reactive protein (CRP) in men with testosterone deficiency. Long-term testosterone therapy in men with TD produced significant reduction in CRP. The data have been reported previously [138–144]

Table 8.5 Relationship between smoking and ED

Study	Number of subjects	Major findings
Polsky et al. [148]	101 men with ED were compared to 234 controls with benign urological conditions	Men with ED were more likely to have been smokers, and a dose–response relationship of cumulative pack years to ED was found
Feldman et al. [23]	513 from the Massachusetts Male Aging Study with no evidence of ED at baseline were surveyed at baseline and 6–10-year follow-up	Cigarette smoking at baseline indicated a significantly increased risk of incident ED during the follow-up period compared to nonsmokers. Passive cigarette exposure also increased the risk of ED
Kupelian et al. [149]	2301 men in the Boston Area Community Health Survey were assessed for smoking exposure by survey	A 20 pack-year or greater history indicated increased rate of ED. Men exposed to passive smoking also had an increased rate of ED
Pourmand et al. [150]	281 men who requested nicotine replacement therapy were surveyed for smoking habits and ED history at baseline and at 1-year follow-up	Men who successfully quit smoking did not have a significantly different rate of ED compared to men who continued to smoke. However, IIEF scores improved in more than 25 % of patients who quit smoking, compared to 0 % of those who continued to smoke
Chan et al. [151]	719 men with ED who were current smokers were randomized to receive either nicotine replacement therapy (NRT) with counseling, NRT alone, or 10 min of advice	Smokers who reported quitting at 6 month follow-up had significantly increased IIEF scores. The type of intervention undertaken did not have an effect of ED outcomes
Harte et al. [152]	65 men who were motivated to quit smoking were enrolled in a smoking cessation program with NRT and assessed physiologically and by self-report on their sexual function at baseline, 8 weeks, and 12 weeks	Men who quit successfully showed significantly increased sexual function and performed better on physiological measures of ability to achieve an erection

valid therapeutic target in the treatment this condition [159]. Although the evidence is limited, the data and the underlying science support this conclusion [158–163]. We should caution, however, that premanent vascular damage and fibroris may be irreversible and limited recovery may be observed by cessation of smoking.

Diabetes Control

It is well recognized that T2DM is a risk factor for developing ED [7, 18, 19]. Diabetes-induced peripheral neuropathy contributes to the etiology of ED. Diabetes control is important for reducing the severity and prevalence of ED. Poor glycemic control contributes to greater risk of ED [164]. Wessells et al. showed that the prevalence of ED was significantly lower in the intensive glucose lowering therapy vs. conventional treatment (12.8 % vs. 30.8 %). The authors concluded that the risk of ED was directly associated with mean HbA1c [165].

Prescription Medications and ED

Several medications affect erectile function [2]. These include antihypertensive agents such thiazide, b-adrenergic receptor blockers, such as propranolol, and alpha 2 receptor agonists such as clonidine do result in diminished erectile function. In addition, psychotropic medication such as antipsychotics also contributes to erectile dysfunction. Agents such as haloperidol and flupenthixol reduce apomorphine-induced erections in

experimental animals. Antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRIs), which are commonly used to treat depression, also contribute to ED. Furthermore, anxiolytics such as benzodiazepines may also interfere with erectile function. In addition, antiandrogens treatment with flutamide or cyproterone resulted in erectile dysfunction [2]. Another class of drugs, the 5 alpha reductase inhibitors (finasteride and dutasteride) used to treat symptoms of benign prostatic hyperplasia and male pattern hair loss (alopecia) were also shown to be associated with increased severity of ED [166].

Summary

As depicted in Fig. 8.8, well-planned and executed changes in lifestyle including increased physical activity and fitness, adopting a healthier diet, reduced alcohol consumption, and cessation of smoking may lead to a reduction in risk factors. This includes improvements in lipid profiles, glycemic control, attenuated inflammation, and increased insulin sensitivity. Such improvements in lifestyle are expected to restore endothelial function, reduce the risk of vascular disease and atherosclerosis, and reduce the risk of CAD resulting in improvement in erectile function. Other approaches that necessitate intervention with pharmacotherapy and/or bariatric surgery have also shown benefits in WL and improvements in overall health and EF. Approaches that require medical intervention need be monitored carefully.

Recommendations and Future Developments

Lifestyle modifications are considered a cornerstone in combating overweight and obesity. However, such an approach is often difficult to maintain over the long term. The ability to achieve modest WL with lifestyle modification is thought to be very limited, at best [167]. An alternative approach is to combine lifestyle changes with pharmacotherapy. This approach provides an alternative to combating overweight and obesity to that of lifestyle changes alone. We propose that lifestyle changes should be coupled with T therapy in obese men with testosterone deficiency and ED. This novel approach offers a safe and effective therapy that produces sustained and sig-

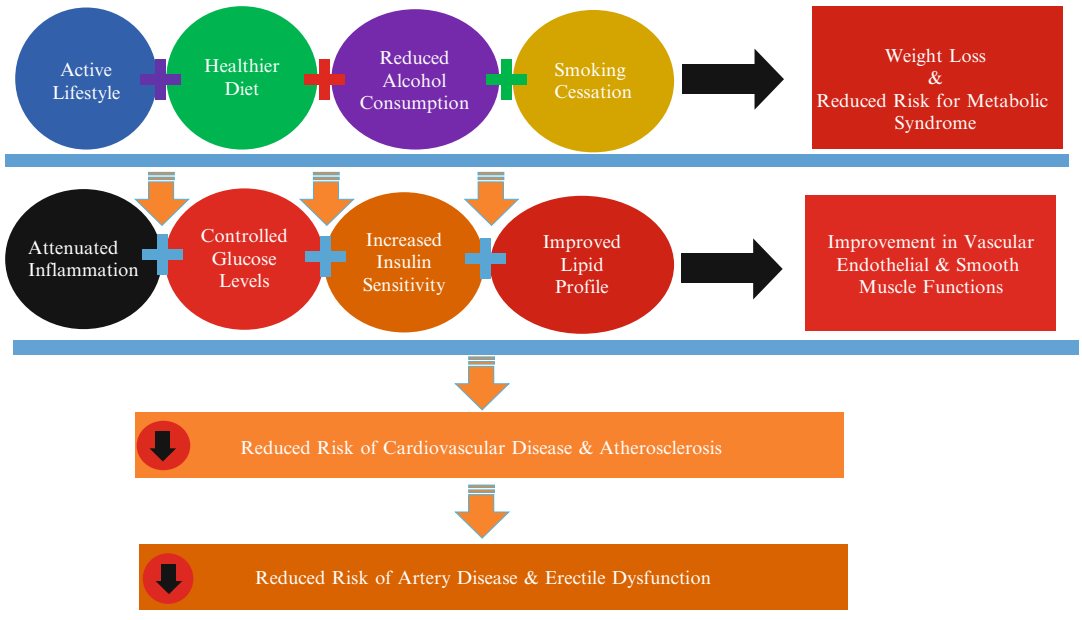

Fig. 8.8 Lifestyle changes may contribute to improvements in erectile function

nificant WL, and ameliorates components of the metabolic syndrome, reducing lipids and improving insulin sensitivity. We believe this approach is effective because T therapy improves mood, increases vigor and energy, and reduces fatigue, leading to increased physical activity. The increased level of physical activity as a result of T therapy would result in increased LBM, reduced FM and sustained and significant WL, and reduction in WC and BMI. Such improvements in body composition would contribute to reducing inflammation and a host of risk factors, leading to improvements in erectile function, thus ameliorating ED. T therapy in obese men with TD is a unique and effective therapeutic approach to management of obesity. The fact that this therapy has been used over the past 7 decades to treat hypogonadism (TD) and is proven to be safe and effective [168, 169] should be an added tool to the armament for combating overweight and obesity and improving overall health and sexual function.

References

1. Krane RJ, Goldstein I, Saenz de Tejada I. Impotence. N Engl J Med. 1989;321(24):1648–59.
2. Sáenz de Tejada I, Angulo J, Cellek S, González-Cadavid N, Heaton J, Pickard R, Simonsen U. Pathophysiology of erectile dysfunction. J Sex Med. 2005;2(1):26–39.
3. Lue TF. Erectile dysfunction. N Engl J Med. 2000;342(24):1802–13.
4. McVary KT. Clinical practice. Erectile dysfunction. N Engl J Med. 2007;357(24):2472–81.
5. Traish AM. Androgens play a pivotal role in maintaining penile tissue architecture and erection: a review. J Androl. 2009;30(4):363–9.
6. de Tejada I, Moroukian P, Tessier J, Kim JJ, Goldstein I, Frohrib D. Trabecular smooth muscle modulates the capacitor function of the penis. Studies on a rabbit model. Am J Physiol. 1991;260(5 Pt 2):H1590–5.
7. Saenz de Tejada I, Goldstein I, Azadzoi K, Krane RJ, Cohen RA. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med. 1989;320(16):1025–30.
8. Nehra A, Goldstein I, Pabby A, Nugent M, Huang YH, de las Morenas A, Krane RJ, Udelson D, Saenz de Tejada I, Moreland RB. Mechanisms of venous leakage: a prospective clinicopathological correlation of corporeal function and structure. J Urol. 1996;156(4):1320–9.
9. Nehra A, Azadzoi KM, Moreland RB, Pabby A, Siroky MB, Krane RJ, Goldstein I, Udelson D. Cavernosal expandability is an erectile tissue mechanical property which predicts trabecular histology in an animal model of vasculogenic erectile dysfunction. J Urol. 1998;159(6):2229–36.
10. Hatzichristou DG, Saenz de Tejada I, Kupferman S, Namburi S, Pescatori ES, Udelson D, Goldstein I. In vivo assessment of trabecular smooth muscle tone, its application in pharmaco-cavernosometry and analysis of intracavernous pressure determinants. J Urol. 1995;153(4):1126–35.
11. 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(1):60–7.
12. Mulhall JP, Anderson M, Parker M. Congruence between veno-occlusive parameters during dynamic infusion cavernosometry: assessing the need for cavernosography. Int J Impot Res. 2004;16(2):146–9.
13. Rajfer J, Rosciszewski A, Mehringer M. Prevalence of corporeal venous leakage in impotent men. J Urol. 1988;140(1):69–71.
14. 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. J Urol. 1997;158(5):1752–8.
15. Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol (Oxf). 2003;58(5):632–8.
16. Wespes E, Rammal A, Garbar C. Sildenafil non-responders: haemodynamic and morphometric studies. Eur Urol. 2005;48(1):136–9.
17. Hwang TI, Chen HE, Tsai TF, Lin YC. Combined use of androgen and sildenafil for hypogonadal patients unresponsive to sildenafil alone. Int J Impot Res. 2006;18(4):400–4.
18. McMahon CG. Erectile dysfunction. Intern Med J. 2014;44:18–26.
19. Koldny RC, Kahn CB, Goldstein HH, Barnett DM. Sexual function in diabetic men. Diabetes. 1973;23:306–9.
20. 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.
21. McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. Diabetologia. 1980;18:279–83.
22. McCulloch DK, Young RJ, Prescott RJ, Campbell IW, Clarke BF. The natural history of impotence in diabetic men. Diabetologia. 1984;26:437–40.
23. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med. 2000;30:328–38.

24. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 2004;291:2978–84.
25. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: results from the health professionals follow up study. Ann Intern Med. 2003;139:161–8.
26. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Thomas S, Bosch JL. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. J Am Geriatr Soc. 2001;49(4):436–42.
27. Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. J Am Coll Cardiol. 2004;43:1405–11.
28. Moreira Jr ED, Bestane WJ, Bartolo EB, Fittipaldi JA. Prevalence and determinants of erectile dysfunction in Santos, southeastern Brazil. Sao Paulo Med J. 2002;120:49–54.
29. 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(2):302–6.
30. Chung WS, Sohn JH, Park YY. Is obesity an underlying factor in erectile dysfunction? Eur Urol. 1999;36(1):68–70.
31. Han TS, Tajar A, O'Neill TW, et al. EMAS group. Impaired quality of life and sexual function in overweight and obese men: the European Male Ageing Study. Eur J Endocrinol. 2011;164:1003–11.
32. Janiszewski PM, Janssen I, Ross R. Abdominal obesity and physical inactivity are associated with erectile dysfunction independent of body mass index. J Sex Med. 2009;6:1990–8.
33. Cheng JY, Ng EM. Body mass index, physical activity and erectile dysfunction: an U-shaped relationship from population-based study. Int J Obes (Lond). 2007;31:1571–8.
34. Corona G, Lee DM, Forti G, et al. EMAS Study Group. Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS). J Sex Med. 2010;7:1362–80.
35. Bajos N, Wellings K, Laborde C, Moreau C, CSF Group. Sexuality and obesity, a gender perspective: results from French national random probability survey of sexual behaviours. BMJ. 2010;340:c2573.
36. Nikoobakht M, Pourkasmaee M, Nasseh H. The relationship between lipid profile and erectile dysfunction. Urol J. 2005;2:40–4.
37. Roumeguere T, Wespes E, Carpentier Y, Hoffmann P, Schulman CC. Erectile dysfunction is associated with a high prevalence of hyperlipidemia and coronary heart disease risk. Eur Urol. 2003;44:355–9.
38. Solomon H, Samarasinghe YP, Feher MD, Man J, Rivas-Toro H, Lumb PJ. Erectile dysfunction and statin treatment in high cardiovascular risk patients. Int J Clin Pract. 2006;60:141–5.
39. Bank AJ, Kelly AS, Kaiser DR, Crawford WW, Waxman B, Schow DA, Billups KL. The effects of quinapril and atorvastatin on the responsiveness to sildenafil in men with erectile dysfunction. Vasc Med. 2006;11:251–7.
40. Dadkhah F, Safarinejad MR, Asgari MA, Hosseini SY, Lashay A, Amini E. Atorvastatin improves the response to sildenafil in hypercholesterolemic men with erectile dysfunction not initially responsive to sildenafil. Int J Impot Res. 2010;22:51–60.
41. El-Sisi AA, Hegazy SK, Salem KA, AbdElkawy KS. Atorvastatin improves erectile dysfunction in patients initially irresponsive to sildenafil by the activation of endothelial nitric oxide synthase. Int J Impot Res. 2013;25:143–8.
42. Gokce MI, Gulpmar O, Ozturk E, Gulec S, Yaman O. Effect of atorvastatin on erectile functions in comparison with regular tadalafil use. A prospective single-blind study. Int Urol Nephrol. 2012;44:683–7.
43. Herrmann HC, Levine LA, Macaluso Jr J, Walsh M, Bradbury D, Schwartz S, Mohler IIIER, Kimmel SE. Can atorvastatin improve the response to sildenafil in men with erectile dysfunction not initially responsive to sildenafil? Hypothesis and pilot trial results. J Sex Med. 2006;3:303–8.
44. Mastalir ET, Carvalhal GF, Portal VL. The effect of simvastatin in penile erection: a randomized, double-blind, placebo-controlled clinical trial (Simvastatin Treatment for Erectile Dysfunction—STED TRIAL). Int J Impot Res. 2011;23:242–8.
45. Trivedi D, Kirby M, Wellsted DM, Ali S, Hackett G, O'Connor B, van Os S. Can simvastatin improve erectile function and health-related quality of life in men aged >40 years with erectile dysfunction? Results of the Erectile Dysfunction and Statins Trial [ISRCTN66772971]. BJU Int. 2012;111:324–33.
46. Nurkalem Z, Yildirimturb O, Ozcan KS, Kul S, Canga Y, Satilmis S, Bozbeyoglu E, Kaya C. The effect of rosuvastatin and atorvastatin on erectile dysfunction in hypercholesterolemic patients. Kardiol Pol. 2014;72(3):275–9.
47. Gokkaya SC, Ozden C, Ozdal OL, Koyuncu HH, Guzel O, Memis A. Effect of correcting serum cholesterol levels on erectile function in patients with vasculogenic erectile dysfunction. Scand J Urol Nephrol. 2008;42:437–40.
48. Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. J Urol. 2004;172:255–8.
49. Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. J Androl. 2009;30(1):10–22.
50. Traish AM, Saad F, Guay A. The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. J Androl. 2009;30(1):23–32.
51. Traish AM, Saad F, Feeley RJ, Guay A. The dark side of testosterone deficiency: III. Cardiovascular disease. J Androl. 2009;30(5):477–94.

52. Rosen RC, Friedman M, Kostis JB. Lifestyle management of erectile dysfunction: The role of cardiovascular and concomitant risk factors. Am J Cardiol. 2005;96:76M–9.
53. Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: crosssectional results from the Massachusetts male aging study. Psychosom Med. 1998;60:458–65.
54. Charansonney OL, Vanhees L, Cohen-Solal A. Physical activity: from epidemiological evidence to individualized patient management. Int J Cardiol. 2014;170:350–7.
55. Maiorino MI, Bellastella G, Esposito K. Lifestyle modifications and erectile dysfunction: what can be expected? Asian J Androl. 2014;17(1):5–10.
56. Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P, Vlachopoulos C. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65(5):968–78.
57. Horasanli K, Boylu U, Kendirci M, Miroglu C. Do lifestyle changes work for improving erectile dysfunction? Asian J Androl. 2008;10(1):28–35.
58. Dunsmuir WD, Holmes SAV. The aetiology and management of erectile, ejaculatory and fertility problems in men with diabetes mellitus. Diabet Med. 1996;13:700–8.
59. De Berardis G, Pellegrini F, Franciosi M, Belfiglio M, Di Nardo B, Greenfield S, et al. Identifying patients with type 2 diabetes with a higher likelihood of erectile dysfunction: the role of the interaction between clinical and psychological factors. J Urol. 2003;169:1422–8.
60. Brunner GA, Pieber TR, Schattenberg S, Ressi G, Wieselmann G, Altziebler S, et al. Erectile dysfunction in patients with type I diabetes mellitus. Wien Med Wochenschr. 1995;145:584–6.
61. Pinnock CB, Stapleton AM, Marshall VR. Erectile dysfunction in the community: a prevalence study. Med J Aust. 1999;171:353–7.
62. Esposito K, Giugliano D. The metabolic syndrome and inflammation: association or causation? Nutr Metab Cardiovasc Dis. 2004;14:228–32.
63. Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA. 2003;289:1799–804.
64. Lee WC, Kim MT, Ko KT, Lee WK, Kim SY, Kim HY, Yang DY. Relationship between serum testosterone and cardiovascular disease risk determined using the Framingham risk score in male patients with sexual dysfunction. World J Mens Health. 2014;32(3):139–44.
65. Kalka D, Domagala ZA, Kowalewski P, Rusiecki L, Koleda P, Marciniak W, Dworak J, Adamus J, Wojcieszczyk J, Pyke E, Pilecki W. Effect of endurance cardiovascular training intensity on erectile dysfunction severity in men with ischemic heart disease. Am J Mens Health. 2015;9(5):360–9.
66. Khoo J, Tian HH, Tan B, Chew K, Ng CS, Leong D, Teo RC, Chen RY. Comparing effects of low- and high-volume moderate-intensity exercise on sexual function and testosterone in obese men. J Sex Med. 2013;10(7):1823–32.
67. Hsiao W, Shrewsberry AB, Moses KA, Johnson TV, Cai AW, Stuhldreher P, Dusseault B, Ritenour CW. Exercise is associated with better erectile function in men under 40 as evaluated by the International Index of Erectile Function. J Sex Med. 2012;9(2):524–30.
68. White JR, Case DA, McWhirter D, Mattison AM. Enhanced sexual behavior in exercising men. Arch Sex Behav. 1990;19:193–209.
69. Hannan JL, Maio MT, Komolova M, Adams MA. Beneficial impact of exercise and obesity interventions on erectile function and its risk factors. J Sex Med. 2009;6 Suppl 3:254–61.
70. Ettala OO, Syvänen KT, Korhonen PE, Kaipia AJ, Vahlberg TJ, Boström PJ, Aarnio PT. High-intensity physical activity, stable relationship, and high education level associate with decreasing risk of erectile dysfunction in 1,000 apparently healthy cardiovascular risk subjects. J Sex Med. 2014;11(9):2277–84.
71. 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. J Urol. 2000;163:460–3.
72. Cheng JY, Ng EM, Ko JS, Chen RY. Physical activity and erectile dysfunction: meta-analysis of population-based studies. Int J Impot Res. 2007;19:245–52.
73. Lamina S, Okoye CG, Dagogo TT. Therapeutic effect of an interval exercise training program in the management of erectile dysfunction in hypertensive patients. J Clin Hypertens (Greenwich). 2009;11:125–9.
74. Korhonen PE, Ettala O, Kautiainen H, Kantola I. Factors modifying the effect of blood pressure on erectile function. J Hypertens. 2015;33(5):975–80.
75. Capogrosso P, Colicchia M, Ventimiglia E, Castagna G, Clementi MC, Suardi N, Castiglione F, Briganti A, Cantiello F, Damiano R, Montorsi F, Salonia A. One patient out of four with newly diagnosed erectile dysfunction is a young man—worrisome picture from the everyday clinical practice. J Sex Med. 2013;10(7):1833–41.
76. Meldrum DR, Gambone JC, Morris MA, Esposito K, Giugliano D, Ignarro LJ. Lifestyle and metabolic approaches to maximizing erectile and vascular health. Int J Impot Res. 2012;24(2):61–8.
77. Maio MT, Hannan JL, Komolova M, Adams MA. Caloric restriction prevents visceral adipose tissue accumulation and maintains erectile function in aging rats. J Sex Med. 2012;9(9):2273–83.
78. Fraga-silva RA, Costa-fraga FP, Faye Y, et al. An increased arginase activity is associated with corpus

cavernosum impairment induced by hypercholesterolemia. J Sex Med. 2014;11(5):1173–81.
79. La Favor JD, Anderson EJ, Hickner RC, Wingard CJ. Erectile dysfunction precedes coronary artery endothelial dysfunction in rats fed a high-fat, high-sucrose, Western pattern diet. J Sex Med. 2013;10(3):694–703.
80. La Favor JD, Anderson EJ, Dawkins JT, Hickner RC, Wingard CJ. Exercise prevents Western diet-associated erectile dysfunction and coronary artery endothelial dysfunction: response to acute apocynin and sepiapterin treatment. Am J Physiol Regul Integr Comp Physiol. 2013;305(4):R423–34.
81. Ryu JK, Shin HY, Song SU, et al. Downregulation of angiogenic factors and their downstream target molecules affects the deterioration of erectile function in a rat model of hypercholesterolemia. Urology. 2006;67(6):1329–34.
82. Tomada I, Negrão R, Almeida H, Neves D. Long-term high-fat consumption leads to downregulation of Akt phosphorylation of eNOS at Ser1177 and upregulation of sirtuin-1 expression in rat cavernous tissue. Age (Dordr). 2014;36(2):597–611.
83. Glina S, Sharlip ID, Hellstrom WJG. Modifying risk factors to prevent and treat erectile dysfunction. J Sex Med. 2013;10:115–9.
84. Moyad MA, Barada JH, Lue TF, Mulhall JP, Goldstein I, Fawzy A, Sexual Medicine Society Nutraceutical Committee. 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(2): 249–57.
85. Moyad MA, Barada JH, Lue TF, Mulhall JP, Goldstein I, Fawzy A, Sexual Medicine Society Nutraceutical Committee. 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(2): 259–73.
86. Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. Int J Impot Res. 2006;18(4):405–10.
87. Esposito K, Giugliano F, Maiorino MI, Giugliano D. Dietary factors, Mediterranean diet and erectile dysfunction. J Sex Med. 2010;7:2338–45.
88. Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. Am J Med. 2015;128(3): 229–38.
89. Esposito K, Giugliano D. Obesity, the metabolic syndrome, and sexual dysfunction in men. Clin Pharmacol Ther. 2011;90(1):169–73.
90. Esposito K, Giugliano F, Ciotola M, De Sio M, D'Armiento M, Giugliano D. Obesity and sexual dysfunction, male and female. Int J Impot Res. 2008;20(4):358–65.
91. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004;292(12):1440–6.
92. Wang F, Dai S, Wang M, Morrison H. Erectile dysfunction and fruit/vegetable consumption among diabetic Canadian men. Urology. 2013;82(6):1330–5.
93. Khoo J, Ling PS, Tan J, Teo A, Ng HL, Chen RY, Tay TL, Tan E, Cheong M. Comparing the effects of meal replacements with reduced-fat diet on weight, sexual and endothelial function, testosterone and quality of life in obese Asian men. Int J Impot Res. 2014;26(2):61–6.
94. Khoo J, Piantadosi C, Duncan R, et al. Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. J Sex Med. 2011;8(10):2868–75.
95. Giugliano F, Maiorino M, Bellastella G, Gicchino M, Giugliano D, Esposito K. Determinants of erectile dysfunction in type 2 diabetes. Int J Impot Res. 2010;22(3):204–9.
96. Meldrum DR, Gambone JC, Morris MA, Meldrum DA, Esposito K, Ignarro LJ. The link between erectile and cardiovascular health: the canary in the coal mine. Am J Cardiol. 2011;108(4):599–606.
97. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012;2(2):1143–211.
98. Booth JN, Bromley LE, Darukhanavala AP, Whitmore HR, Imperial JG, Penev PD. Reduced physical activity in adults at risk for type 2 diabetes who curtail their sleep. Obesity (Silver Spring). 2012;20(2):278–84.
99. Sansone A, Romanelli F, Gianfrilli D, Lenzi A. Endocrine evaluation of erectile dysfunction. Endocrine. 2014;46(3):423–30.
100. Sgrò P, Romanelli F, Felici F, Sansone M, Bianchini S, Buzzachera CF, Baldari C, Guidetti L, Pigozzi F, Lenzi A, Di Luigi L. Testosterone responses to standardized short-term sub-maximal and maximal endurance exercises: issues on the dynamic adaptive role of the hypothalamic-pituitary-testicular axis. J Endocrinol Invest. 2014;37(1):13–24.
101. Traish AM. Adverse health effects of testosterone deficiency (TD) in men. Steroids. 2014;88:106–16.
102. Traish AM. Outcomes of testosterone therapy in men with testosterone deficiency (TD): part II. Steroids. 2014;88:117–26.
103. Behr-Roussel D, Darblade B, Oudot A, Compagnie S, Bernabé J, Alexandre L, Giuliano F. Erectile dysfunction in hypercholesterolemic atherosclerotic apolipoprotein E knockout mice. J Sex Med. 2006;3(4):596–603.
104. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011;171(20): 1797–803.

105. Szostak J, Laurant P. The forgotten face of regular physical exercise: a 'natural' anti-atherogenic activity. Clin Sci (Lond). 2011;121(3):91–106.
106. Padilla J, Simmons GH, Bender SB, Arce-Esquivel AA, Whyte JJ, Laughlin MH. Vascular effects of exercise: endothelial adaptations beyond active muscle beds. Physiology (Bethesda). 2011;26(3):132–45.
107. Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. Physiol Rev. 2012;92(1):157–91.
108. Boden WE, Franklin B, Berra K, Haskell WL, Calfas KJ, Zimmerman FH, Wenger NK. Exercise as a therapeutic intervention in patients with stable ischemic heart disease: an underfilled prescription. Am J Med. 2014;127(10):905–11.
109. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology (Bethesda). 2013;28(5):330–58.
110. Lancaster GI, Febbraio MA. The immunomodulating role of exercise in metabolic disease. Trends Immunol. 2014;35(6):262–9.
111. Martin SA, Atlantis E, Lange K, Taylor AW, O'Loughlin P, Wittert GA, Florey Adelaide Male Ageing Study. Predictors of sexual dysfunction incidence and remission in men. J Sex Med. 2014;11(5):1136–47.
112. Reis LO, Favaro WJ, Barreiro GC, de Oliveira LC, Chaim EA, Fregonesi A, Ferreira U. Erectile dysfunction and hormonal imbalance in morbidly obese male is reversed after gastric bypass surgery: a prospective randomized controlled trial. Int J Androl. 2010;33:736–44.
113. Kun L, Pin Z, Jianzhong D, Xiaodong H, Haoyong Y, Yuqian B, Hongwei Z. significant improvement of erectile function after Roux-en-Y gastric bypass surgery in obese Chinese men with erectile dysfunction. Obes Surg. 2015;25(5):838–44.
114. Mora M, Aranda GB, de Hollanda A, Flores L, Puig-Domingo M, Vidal J. Weight loss is a major contributor to improved sexual function after bariatric surgery. Surg Endosc. 2013;27(9):3197–204.
115. Rosenblatt A, Faintuch J, Cecconello I. Sexual hormones and erectile function more than 6 years after bariatric surgery. Surg Obes Relat Dis. 2013;9(5):636–40.
116. Wing RR, Rosen RC, Fava JL, Bahnson J, Brancati F, Gendrano Iii IN, Kitabchi A, Schneider SH, Wadden TA. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. J Sex Med. 2010;7(1 Pt 1):156–65.
117. Dallal RM, Chernoff A, O'Leary MP, Smith JA, Braverman JD, Quebbemann BB. Sexual dysfunction is common in the morbidly obese male and improves after gastric bypass surgery. J Am Coll Surg. 2008;207(6):859–64.
118. Collins CE, Jensen ME, Young MD, Callister R, Plotnikoff RC, Morgan PJ. Improvement in erectile function following weight loss in obese men: the SHED-IT randomized controlled trial. Obes Res Clin Pract. 2013;7(6):e450–4.
119. Esposito K, Ciotola M, Giugliano F, Maiorino MI, Autorino R, De Sio M, Giugliano G, Nicoletti G, D'Andrea F, Giugliano D. Effects of intensive lifestyle changes on erectile dysfunction in men. J Sex Med. 2009;6(1):243–50.
120. Chitaley K, Kupelian V, Subak L, Wessells H. Diabetes, obesity and erectile dysfunction: Field overview and research priorities. J Urol. 2009;182(6 suppl):S45–50.
121. Vignozzi L, Filippi S, Comeglio P, Cellai I, Morelli A, Rastrelli G, Maneschi E, Mannucci E, Maggi M. Metformin in vitro and in vivo increases adenosine signaling in rabbit corpora cavernosa. J Sex Med. 2014;11(7):1694–708.
122. Esposito K, Giugliano D. Obesity, the metabolic syndrome, and sexual dysfunction. Int J Impot Res. 2005;17(5):391–8.
123. Esposito K, Giugliano F, Martedì E, Feola G, Marfella R, D'Armiento M, Giugliano D. High proportions of erectile dysfunction in men with the metabolic syndrome. Diabetes Care. 2005;28(5):1201–3.
124. Maiorino MI, Bellastella G, Esposito K. Diabetes and sexual dysfunction: current perspectives. Diabetes Metab Syndr Obes. 2014;7:95–105.
125. Maiorino MI, Bellastella G, Petrizzo M, Della Volpe E, Orlando R, Giugliano D, Esposito K. Circulating endothelial progenitor cells in type 1 diabetic patients with erectile dysfunction. Endocrine. 2015;49(2):415–21.
126. Camacho EM, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, Tajar A, Bartfai G, Boonen S, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Keevil B, Lean ME, Pendleton N, Punab M, Vanderschueren D, Wu FC, EMAS Group. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. Eur J Endocrinol. 2013;168(3):445–55.
127. Traish AM. Testosterone and weight loss: the evidence. Curr Opin Endocrinol Diabetes Obes. 2014;21(5):313–22.
128. Young MD, Collins CE, Callister R, Plotnikoff RC, Doran CM, Morgan PJ. The SHED-IT weight loss maintenance trial protocol: a randomised controlled trial of a weight loss maintenance program for overweight and obese men. Contemp Clin Trials. 2014;37(1):84–97.
129. Aguiar EJ, Morgan PJ, Collins CE, Plotnikoff RC, Young MD, Callister R. The PULSE (Prevention Using LifeStyle Education) trial protocol: a randomised controlled trial of a Type 2 diabetes Prevention programme for men. Contemp Clin Trials. 2014;39(1):132–44.
130. Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS. The role of exercise and physical activ-

ity in weight loss and maintenance. Prog Cardiovasc Dis. 2014;56(4):441–7.
131. Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, Niskanen L, Rasmussen MF, Rissanen A, Rössner S, Savolainen MJ, Van Gaal L, NN8022-1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond). 2012;36(6):843–54.
132. Ioannides-Demos LL, Piccenna L, McNeil JJ. Pharmacotherapies for obesity: past, current, and future therapies. J Obes. 2011;2011:179674.
133. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2014;99(1):14–23.
134. Gadde KM. Current pharmacotherapy for obesity: extrapolation of clinical trials data to practice. Expert Opin Pharmacother. 2014;15(6):809–22.
135. Nauck M, Frid A, Hermansen K, Thomsen AB, During M, Shah N, Tankova T, Mitha I, Matthews DR. Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. Diabetes Obes Metab. 2013;15(3):204–12.
136. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. JAMA Surg. 2014;149(3):275–87.
137. Calderón B, Galdón A, Calañas A, Peromingo R, Galindo J, García-Moreno F, Rodriguez-Velasco G, Martín-Hidalgo A, Vazquez C, Escobar-Morreale HF, Botella-Carretero JI. Effects of bariatric surgery on male obesity-associated secondary hypogonadism: comparison of laparoscopic gastric bypass with restrictive procedures. Obes Surg. 2014;24(10):1686–92.
138. Saad F, Haider A, Doros G, Traish A. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. Obesity (Silver Spring). 2013;21(10):1975–81.
139. Haider A, Saad F, Doros G, Gooren L. Hypogonadal obese men with and without diabetes mellitus type 2 lose weight and show improvement in cardiovascular risk factors when treated with testosterone: an observational study. Obes Res Clin Pract. 2014;8(4):e339–49.
140. Yassin A, Doros G. Testosterone therapy in hypogonadal men results in sustained and clinically meaningful weight loss. Clin Obes. 2013;3(3-4):73–83.
141. Haider A, Yassin A, Doros G, Saad F. Effects of long-term testosterone therapy on patients with "diabesity": results of observational studies of pooled analyses in obese hypogonadal men with type 2 diabetes. Int J Endocrinol. 2014;2014:683515.
142. Francomano D, Ilacqua A, Bruzziches R, Lenzi A, Aversa A. Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. Urology. 2014;83(1):167–73.
143. Yassin DJ, Doros G, Hammerer PG, Yassin AA. Long-term testosterone treatment in elderly men with hypogonadism and erectile dysfunction reduces obesity parameters and improves metabolic syndrome and health-related quality of life. J Sex Med. 2014;11(6):1567–76.
144. Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. Int J Endocrinol. 2014;2014:527470.
145. Traish AM, Haider A, Doros G, Saad F. Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. Int J Clin Pract. 2014;68(3):314–29.
146. Saad F, Yassin A, Haider A, Doros G, Gooren L. Elderly men over 65 years of age with late-onset hypogonadism benefit as much from testosterone treatment as do younger men. Korean J Urol. 2015;56(4):310–7.
147. Saad F, Gooren L. Late onset hypogonadism of men is not equivalent to the menopause. Maturitas. 2014;79:52–7.
148. Polsky JY, Aronson KJ, Heaton JP, Adams MA. Smoking and other lifestyle factors in relation to erectile dysfunction. BJU Int. 2005;96(9):1355–9.
149. Kupelian V, Link CL, Mckinlay JB. Association between smoking, passive smoking, and erectile dysfunction: results from the Boston Area Community Health (BACH) Survey. Eur Urol. 2007;52(2):416–22.
150. Pourmand G, Alidaee MR, Rasuli S, Maleki A, Mehrsai A. Do cigarette smokers with erectile dysfunction benefit from stopping? A prospective study. BJU Int. 2004;94(9):1310–3.
151. Chan SS, Leung DY, Abdullah AS, et al. Smoking-cessation and adherence intervention among Chinese patients with erectile dysfunction. Am J Prev Med. 2010;39(3):251–8.
152. Harte CB, Meston CM. Association between smoking cessation and sexual health in men. BJU Int. 2012;109(6):888–96.
153. Cao S, Gan Y, Dong X, Liu J, Lu Z. Association of quantity and duration of smoking with erectile dysfunction: a dose-response meta-analysis. J Sex Med. 2014;11(10):2376–84.
154. Tengs TO, Osgood ND. The link between smoking and impotence: two decades of evidence. Prev Med. 2001;32(6):447–52.
155. Cao S, Yin X, Wang Y, Zhou H, Song F, Lu Z. Smoking and risk of erectile dysfunction: systematic review of observational studies with meta-analysis. PLoS One. 2013;8(4), e60443.
156. Dorey G. Is smoking a cause of erectile dysfunction? A literature review. Br J Nurs. 2001;10:455–65.

157. Tostes RC, Carneiro FS, Lee AJ, et al. Cigarette smoking and erectile dysfunction: focus on NO bioavailability and ROS generation. J Sex Med. 2008;5(6):1284–95.
158. Murohara T, Kugiyama K, Ohgushi M, Sugiyama S, Yasue H. Cigarette smoke extract contracts isolated porcine coronary arteries by superoxide anion-mediated degradation of EDRF. Am J Physiol. 1994;266(3 Pt 2):H874–80.
159. Mcvary KT, Carrier S, Wessells H. Smoking and erectile dysfunction: evidence based analysis. J Urol. 2001;166(5):1624–32.
160. Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? Am J Epidemiol. 1994;140(11):1003–8.
161. Higman DJ, Strachan AM, Buttery L, Hicks RC, Springall DR, Greenhalgh RM, Powell JT. Smoking impairs the activity of endothelial nitric oxide synthase in saphenous vein. Arterioscler Thromb Vasc Biol. 1996;16(4):546–52.
162. Rosen RJ. Smoking cessation. Cornerstone of prevention in primary care. N C Med J. 1995; 56(1):53–5.
163. Mirone V, Imbimbo C, Bortolotti A, Di Cintio E, Colli E, Landoni M, Lavezzari M, Parazzini F. Cigarette smoking as risk factor for erectile dysfunction: results from an Italian epidemiological study. Eur Urol. 2002;41(3):294–7.
164. Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. J Urol. 2000;163:788–91.
165. Wessells H, Penson DF, Cleary P, Rutledge BN, Lachin JM, McVary KT, Schade DS, Sarma AV. Effect of intensive glycemic therapy on EFin men with type 1 diabetes. J Urol. 2011;185:1828–34.
166. Traish AM, Mulgaonkar A, Giordano N. The dark side of 5α-reductase inhibitors' therapy: sexual dysfunction, high Gleason grade prostate cancer and depression. Korean J Urol. 2014;55(6):367–79.
167. Ekkekakis P, Vazou S, Bixby WR, and Georgiadis E. The mysterious case of the public health guidelines that (almost) entirely ignored: call for a research agenda on the causes of the extreme avoidance of physical activity in obesity. Obes Rev. 2016; 17:313–29.
168. Aub JC. The use of testosterone. New Engl J Med. 1940;222:877–81.
169. Aub JC, Kety SS. Recent advances in testosterone therapy. New Engl J Med. 1943; 228:338–43.

9 Cardiovascular Issues in the Treatment of Erectile Dysfunction

Graham Jackson, Michael Kirby, and Geoffrey Hackett

Introduction

Erectile dysfunction (ED) is common as is cardiovascular disease (CVD). As both affect similar age groups, it is not surprising that the two conditions frequently coexist [1, 2]. Both a high incidence and prevalence of ED worldwide are currently estimated to affect up to 150 million men, and as the population is aging, by 2025 the prevalence is expected to increase to 300 million men [3].

Importantly, ED is now recognised for most men to be of vascular aetiology with endothelial dysfunction the common denominator. ED often precedes CVD and is also present in men with known CVD, leading to the concept that a man with ED and no CVD symptoms is a cardiac or vascular patient until proved otherwise, and a man with known CVD should be routinely asked about his erectile function [4]. As ED is known to predict vascular disease and *mortality*, it emphasises the need to address ED as early as possible to not only treat the ED but to deal with the coronary risk [5, 6].

Risk Factors

In the previous chapter, lifestyle changes are very extensively covered. The modifiable risk factors for CVD are shared with ED. They include hypertension, hyperlipidaemia, diabetes, obesity, lack of physical exercise, cigarette smoking, poor diet, excess alcohol consumption and psychological stress, including depression [4]. Of clinical importance is the recognition that ED is an independent marker in addition to these conventional risk factors [4]. In a systemic review and meta-analysis including six clinical trials and 740 participants from four countries, lifestyle modification and pharmacological therapy demonstrated a statistically significant improvement in sexual function—changes that historically have also been shown to reduce CVD risk and mortality [7]. Men with ED therefore provide us with an opportunity to identify CVD risk factors and initiate targeted risk reduction lifestyle changes. By reducing the risk of ED, this may be an unexplored motivation to tackle CVD risk factors—adding life to years as well as years to life.

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The importance of risk factor reduction remains fundamental to the overall vascular good health of the individual and that includes sexual vascular health [2]. The triad of ED, endothelial dysfunction and CVD emphasises the need for ED to be included in all CVD risk calculators [8].

Interestingly the conditions that link the risk factors for coronary artery disease (CAD), CVD and ED include a pro-inflammatory state that results in endothelial dysfunction by decreasing the availability of nitric oxide (NO). It has been suggested that lifestyle changes decrease low-grade inflammation and thereby benefit both ED and vascular disease. Whatever the mechanism, promotion of a healthy lifestyle is strongly recommended for men in general and for men with ED in particular [2].

ED and CVD: Examining the Link

The vascular endothelium plays a key role in the critical association between erectile dysfunction (ED) and cardiovascular disease (CVD), as it is intimately involved in the regulation of the circulation. Hypertension, ischaemic heart disease, hypercholesterolaemia and diabetes all lead to abnormalities in the vascular smooth muscle cells and the extracellular matrix. The endothelial cell dysfunction precedes the formation of atherosclerotic plaques and is common in patients with CVD and those with diabetes. Patients with diabetes have endothelial dysfunction and an increased risk of developing cardiovascular complications. The role of impaired endothelial-dependent vasodilation by nitric oxide (NO) is well documented in coronary artery disease (CAD) and in conditions such as hypertension, diabetes and dyslipidaemia [9].

In 1999, the link between ED and CVD was first discussed and it was concluded that "ED is a clinically important complication of cardiovascular disease and should be asked about and treated accordingly" [10].

In 2001, two publications raised the question "Is ED (erectile dysfunction) a marker for silent (asymptomatic) CAD?" This was followed by the recognition that ED precedes CAD in about two-thirds of cases [11, 12], with the mean time interval from the development of ED to symptoms of coronary ischaemia being in the region of 2–3 years. For a cardiovascular event such as a myocardial infarction or a stroke, it is more like 3–5 years. Longer time frames may also occur [4, 6]. This important clinical link was further reinforced by the fact that, when comparing various degrees of CAD, the more severe the CAD, the more severe the ED [13].

In addition to this, the size of the vessel matters. Penile arteries are 1–2 mm in diameter, whereas coronary arteries are larger at 3–4 mm. Therefore endothelial dysfunction and plaque burden in the smaller vessels would be symptomatic, i.e., producing ED, before the similar process in the larger vessels affects blood flow.

Significant obstruction (50–70 %) of the coronary arteries needs to occur before symptoms lead the clinician to the diagnosis. Unfortunately, asymptomatic lipid-rich plaques in the vessels are vulnerable to rupture, leading to the assumption that ED might predict an acute coronary syndrome or death, since we know that many acute events, including sudden death, occur without any previous warning symptoms [14].

Two large meta-analyses have added weight to the hypothesis that ED predicts the risk or CVD, as well as cardiovascular and all-cause mortality [15, 16] (Table 9.1). Given that endothelial dysfunction precedes the development of atherosclerotic plaques, the problem occurs at a cellular level and leads to impaired bioavailability of NO. A further systematic review of ED and CVD [16] concluded that they should be regarded as two different manifestations of the same systemic disorder and that ED usually precedes CVD onset and it might be considered an early marker of symptomatic CVD. Therefore, from a clinical standpoint, because ED precedes CVD, it can be used as an early warning marker to identify men at higher risk of developing CVD events. These ED patients at high risk of CVD should undergo detailed cardiologic assessment and receive intensive treatment of risk factors. In clinical practice, the fundamental question in men with ED is whether there is CVD especially asymptomatic CAD and how it is then detected.

Table 9.1 Relative risks for men with ED vs. no ED

		95 % Confidence interval	*p*
First analysis [15]			
Overall relative risks	1.48	1.25–1.4	<0.001
CAD	1.46	1.31–1.63	<0.001
Stroke	1.35	1.19–1.54	<0.001
All-cause mortality	1.19	1.05–1.34	0.005
Second analysis [16]			
Overall relative risks	1.44	1.27–1.63	<0.001
CAD (MI)	1.62	1.34–1.96	<0.001
Stroke	1.39	1.23–1.57	<0.001
All-cause mortality	1.25	1.12–1.39	<0.001

CAD coronary artery disease

The Patient's Assessment

From a cardiovascular perspective, the medical assessment should include blood pressure measurement, fasting glucose, HbA1c and lipid profile, waist circumference, thyroid function and testosterone (before 11 am). Testosterone deficiency is often missed, and because it is frequently associated with type II diabetes or chronic illness such as heart failure and renal disease of hypertension, it should not be excluded.

The Princeton III Consensus recommendations for the management of ED and cardiovascular disease have emphasised that the link between ED and CVD which may be asymptomatic could well benefit from cardiovascular reduction [2]. Finally, Martin Miner and colleagues have concluded that all men with vasculogenic erectile dysfunction require a cardiovascular workup [17]. The body of evidence, therefore, supports cardiovascular risk reduction and risk factor management in all men with vasculogenic ED.

In a prospective study, GJ addressed the fundamental question in men with ED and no cardiac symptoms as to whether there is CVD, especially asymptomatic CAD, and how to detect it [7]. Exercise electrocardiography depends on identifying flow-limiting lesions of at least 50–70 % stenosis as will stress echocardiography or myocardial perfusion scanning [3]. This is important given that ED predicts acute coronary syndromes and all-cause mortality which in 50–60 % of cases are not associated with any preceding cardiac symptoms. ED becomes the missing marker of increased risk especially in younger men at intermediate risk (5–10 %) and is simple to enquire about.

In this series out-patient multidetector computed tomography (MDCT) demonstrated asymptomatic CAD in 60 out of 65 men with noncalcified plaques in seven men. This fits with the pathophysiological concept of plaque rupture explaining the acute events and establishes ED as a cardiovascular equivalent with a man with ED and no cardiac symptoms being considered a CVD patient until proven otherwise.

Depending on location, not every man with ED will have access to MDCT. A reasonable approach is to use calcium screening (1–2 mSU X rays compared with CXR 0.02) in those most at risk, especially men ages 30–60 years, but preferably MDCT (5–20 mSU) to detect soft and/or noncalcified plaque. Alternatively a policy of aggressive risk reduction in all identified men with ED (ask routinely) and elective investigation when clinically appropriate could be pursued, but this demands detailed and regular follow-up. An ideal algorithm is seen in Fig. 9.1.

The assessment of vascular risk in men with ED and the role of the cardiologist and general physician have recently been reviewed. Whilst it is certainly true that biomarkers have an important role to play, with the advent of MDCT, a relatively noninvasive out-patient approach to the anatomy arteries, we believe the way forward is that all men with erectile dysfunction should undergo this out-patient procedure.

Key Points

1. ED is a predictor of coronary artery disease.
2. ED is an independent marker of events.
3. ED should be asked about routinely.
4. ED may trigger cardiac risk reduction with long-term benefits.
5. ED may identify patients with significant coronary disease subject for intervention.

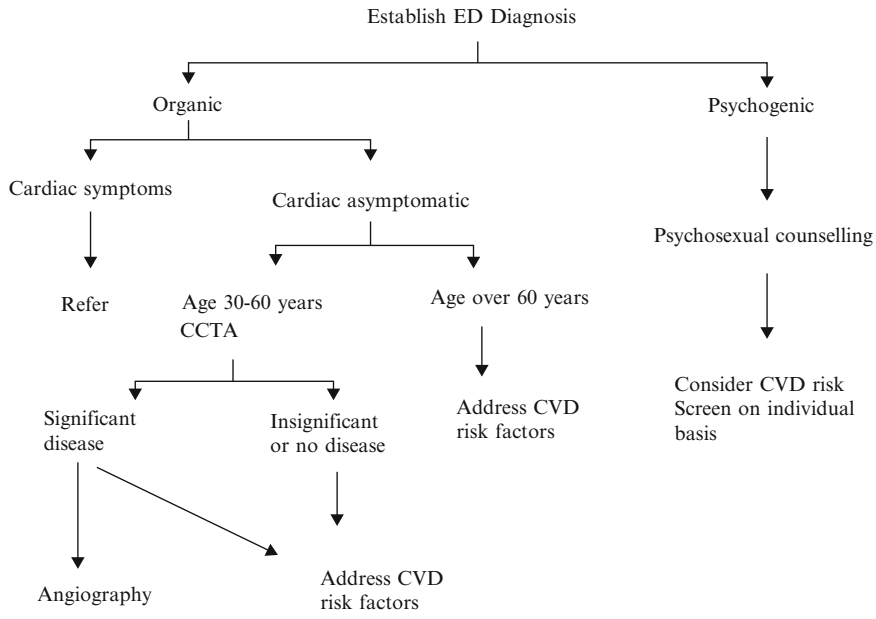

Fig. 9.1 Investigative algorithm cardiovascular issues in the treatment of erectile dysfunction

Testosterone: Its Replacement and Cardiovascular Safety

Recently there has been controversy concerning testosterone replacement therapy (TRT) increasing the risk of adverse cardiovascular events. Two retrospective studies and one trial using high and inappropriate doses of testosterone in elderly patients became the focus of attention in spite of many clinical trials, including randomised trials, which showed that TRT conferred no cardiovascular risk.

An expert opinion from Professor Maggi's unit entitled "Cardiovascular risk associated with testosterone-boosting medications: systemic review and meta-analysis" [18] concluded that there was no causal role between TRT and cardiovascular events. Their results were in agreement with a large body of literature for the past 20 years, which supported the use of TRT in men who were hypogonadal improving their metabolic profile, reducing fat and increasing lean muscle mass which would ultimately reduce the risk of heart disease.

The controversy has been reviewed by Morgentaler, in an invited commentary, entitled "Testosterone, cardiovascular risk and hormonophobia" [19], and he concluded that the use of weak studies as proof of danger indicates a cultural, that is, a nonscientific force. He went on to state that, after reviewing the articles, "The true outrage is that social forces and hysteria have combined to deprive men of a useful treatment without regard for medical science." Morgentaler concluded that a wealth of evidence, collated over several decades, indicated that low testosterone levels are associated with increased risk and that higher androgynous testosterone as well as testosterone replacement itself appears to be beneficial for cardiovascular mortality and risk. The adverse discussions and comments almost certainly reflect the lack of content justifying the headlines, rather like the calcium antagonist saga. However, by publishing these papers, the impact factor of the journals has been significantly increased. Impact factor alone should not be the main determinant for publication because of potential adverse effects on the patients and the media. It is the

responsibility of editors to place the publication of these articles in the correct context.

The two studies that have attracted most attention are both retrospective. The Vigen et al. study [20] compared two groups: those receiving TRT and those who did not. There was a complicated statistical analysis using over 50 variables, which changed a positive effect or TRT with lower CV events to an adverse result. Importantly, there was no evidence that all patients were diagnosed with hypogonadism and 17.6 % received only one prescription. The mean testosterone level in those that continued on treatment was subtherapeutic, and the authors also admitted women had been included in the analysis. (Beware statistics!)

The Finkle et al. study [21] , which again was retrospective, used data on 56,000 testosterone prescriptions in California compared to reporting of myocardial infarction in the first 3 months with either the same patients in the 12 months prior to the prescription or a cohort of men receiving phosphodiesterase type 5 (PDE5) inhibitors. They reported an increased risk of myocardial infarction on TRT compared with the other group. No data were given on whether hypogonadism was diagnosed before initiation of therapy or if testosterone levels had been performed nor testosterone levels on treatment. The comparator groups were not appropriate. The use of nitrates associated with more severe CVD is contraindicated with PDE5 inhibitors, so the latter group would potentially have been a healthier cohort in respect to pre-existing disease.

There is therefore a long history of studies investigating testosterone and cardiovascular risk, in particular mortality, and they reveal important associations with low testosterone and mortality with higher serum testosterone appearing to be protective. Although no definitive *prospective* studies have yet been performed, substantial literature accumulated over several decades has failed to provide any credible risk that testosterone therapy is associated with increased cardiac mortality or major cardiovascular events. Therefore there is no need to change the conclusions of the editorial "Testosterone Deficiency Syndrome (TDS) and the heart" [22] published in 2010 in the European Heart Journal. The European Medicines Agency (EMA) could find no consistent evidence that the use of testosterone in men with hypogonadism increased the risk of cardiovascular problems. After a review of all the literature, it is the conclusion that the benefits of testosterone continue to outweigh its risks, but the EMA goes on to recommend TRT has to be confirmed as being appropriate by measuring the baseline level.

Key Points

1. Low testosterone is associated with increased mortality and increased cardiovascular risk.
2. Testosterone levels should always be measured before TRT is considered.
3. There is no need to be unduly concerned about TRT in appropriately selected patients.
4. Long-term monitoring and current ongoing trials are essential with regard to the continuing management of testosterone.

References

1. Quyyumi AA, Dakak N, Mulcahyd H, et al. Nitric oxide activity in the atherosclerotic human coronary circulation. J Am Coll Cardiol. 1997;29:308–17.
2. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus Recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87:766–78.
3. Jackson G. Erectile dysfunction and cardiovascular disease. Arab J Urol. 2012;11(3):212–6.
4. Jackson G, Boon N, Eardley I, Kirby M, et al. Erectile dysfunction and coronary disease prediction: evidence based guidance and consensus. Int J Clin Pract. 2010;64:848–57.
5. Araujo AB, Travison TG, Ganz P, et al. Erectile dysfunction and mortality. J sex Med. 2009;6:2445–54.
6. Hodges LD, Kirby M, Solanki J, et al. The temporal relationship between erectile dysfunction and cardiovascular disease. Int J Clin Pract. 2007;61:2019–25.
7. Gupta BP, Murad MH, Clifton MM, et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011;171:1797–803.
8. Vlachopoulos C, Aznaouridis K, Ioakeimidis N, et al. Unfavourable endothelial and inflammatory state in

erectile dysfunction patients with or without coronary artery disease. Eur Heart J. 2006;27:2640–8.
9. Maas R, Schwedhelm E, Albsmeier J, et al. The pathophysiology of erectile dysfunction related to endothelial dysfunction and mediators of vascular function. Vasc Med. 2002;7(3):213–25.
10. Jackson G. Erectile dysfunction and cardiovascular disease. Int J CLin Pract. 1999;53:363–8.
11. O'Kane PD, Jackson G. Erectile dysfunction: is there a silent obstructive coronary artery disease? Int J Clin Pract. 2001;55:219–20.
12. Kirby M, Jackson G, Betteridge J, et al. Is erectile dysfunction a marker for cardiovascular disease? Int J Clin Pract. 2001;55:614–8.
13. Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J. 2006;27:2632–9.
14. Jackson G, Nehra A, Miner M, et al. The assessment of vascular risk in men with ED, the role of the cardiologist and the general physician. Int J Clin Pract. 2013;67(11):1163–72.
15. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Caridol. 2011;58:1378–85.
16. Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, et al. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes. 2013;6:1–11.
17. Miner M, Nehra A, Jackson G, et al. All men with vasculogenic erectile dysfunction require a cardiovascular workup. Am J Med. 2014;127(3):174–82.
18. Corona G, Maseroli E, Rastrelli G, et al. Expert Opin. 2014;13(10):1327–51.
19. Morgentaler A. Testosterone, cardiovascular risk and hormonophobia. J Sex Med. 2014;6:1362–6.
20. Vigen R, O'Donnell CL, Baron A, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013;310:1829–36.
21. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014;9:1–7.
22. Jackson G. Testosterone deficiency syndrome (TDS) and the heart. Eur Heart J. 2010;31:1436–7.

Alternative and Internet Drugs that Affect Sexual Function

10

Jonathan Israel and Eric L. Laborde

Introduction

For thousands of years, humans have been using plants for medicinal purposes. There is evidence that the Egyptians used saw palmetto to help with voiding dysfunction 3500 years ago [1], while the Greeks used St John's wort for depression in the fifth century BC [2], and the Chinese have a rich history of using complex herbal treatments dating back to the time of the Yellow Emperor in 2700 BC [3]. In the United States during the 1820s, two thirds of the US pharmacopeia were botanical substances. It was not until the early twentieth century that synthetic drugs began replacing these traditional treatments [2]. Although synthetic drugs now make up a greater share of the market, people today still rely on "alternative" and "natural" medications.

With the advent of the Internet, patients are able to search and oftentimes order not only herbal treatments for erectile dysfunction (ED) but also trade-named pharmaceuticals. This chapter will focus on how the Internet affects ED treatment and several of the commonly used herbal supplements.

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Epidemiology

There is now a renewed interest in using complementary and alternative medicines to treat medical conditions. Nearly one in five people now report using herbal products in the United States [4]. There are over one thousand companies that are making these products with annual revenues in excess of 60 billion dollars. Per one report, there are over 29,000 herbal supplements and the market is growing [5]. It is not surprising to see that these products are being sold from all over the world. India, Canada, the United States, France, Britain, and China all share a piece of the market. Considering that drug stores, supermarkets, warehouse buying clubs, natural food stores, health professionals, and the Internet are all sources of sale for these products, getting a true picture of overall sales is difficult.

Regulation

Initially, medicinal herbs were included in the US national formulary. However, in 1962 due to complications of thalidomide in causing birth defects, congress passed the Kefauver-Harris Drug Amendment. This amendment was responsible for increasing the proof of safety and efficacy of all prescription drugs. It also reassigned herbal medicines to a category labeled "food

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supplements" which had more lenient thresholds for evidence of safety compared to pharmaceutical drugs. In 1994 the government passed the Dietary Supplement Health and Education Act (DSHEA). This act defined dietary supplements as a product containing one or more of the following: a vitamin, mineral, amino acid, herb, other botanical, concentrate, metabolite, constituent, or extract. It required labels of dietary supplements to state "This product in not intended to diagnose, treat, cure, or prevent any disease." However, product labels were still allowed to make health claims, such as "promotes prostate health" or "supports the circulatory system." The act also stated that the efficacy, safety, and quality of the product did not need to be determined by supplement manufacturer prior to release to the public. The side effect post-marketing also did not need to be reported to FDA, and it shifted the burden of proving that a product is unsafe or ineffective onto the FDA [6]. It, therefore, made it easier for manufacturers to get their product to the public.

Because of these changes, there is ample opportunity for problems with supplements and counterfeit drugs. These drugs can contain too much, too little, or none of the active ingredient. There can also be contaminants or other substances that should not be in the product. Additionally, manufactures can make false claims about the efficacy of an herbal treatment or supplement. It has even been shown that ED treatment products that are supposed to be "natural" or "herbal" can often (81 % of the time) contain pharmaceutical grade phosphodiesterase type 5 inhibitors [7].

One group evaluated 44 products from 12 separate companies using DNA bar coding to compare the ingredients on the label to the ingredients in the product. Only forty-eight percent had authentic main ingredient listed and present in the product, 59 % had plant species that were not found on the label, and 33 % contained fillers which had no active ingredient. Only 2 of 12 companies provided authentic products. One quarter of the companies had ingredients that could not even be identified with DNA bar coding [8].

In another investigation of contamination in 131 herbal tea products, Stoeckle et al. were only able to authenticate 58 % of the products, and they showed 33 % were contaminated with other ingredients [9]. Another group looking at a marketplace survey of 40 dietary supplements labeled "Black cohash" found that 25 % products were substituted with another closely related plant species [10].

Unfortunately, because of this unregulated market, there can be disastrous consequences. In Argentina two women died from counterfeit iron injections [11] In a New England Journal of Medicine article, the authors found that in 260 Asian patient medicines, 25 % contained high levels of heavy metals [12], and in 2002 more than 190,000 deaths were associated to diethylene glycol contamination of paracetamol syrup [13]. The Department of Health and Human Services has even stated that the true frequency of adverse side effects is probably underreported. They state that they are probably detecting <1 % of all incidents [14]. Not surprisingly, organizations such as the Institute of Medicine and consumer advocacy groups have called for reform of the DSHEA [15].

Impact on Men's Sexual Health

Even with all the aforementioned risks of taking "natural products," there is still a market for these products. From a men's health perspective, one of the most common uses of a "natural product" is to treat erectile dysfunction. One of the primary drivers for this is cost. Prescription phosphodiesterase type 5 inhibitors (PDE5is) can cost 20–40 times more than their online counterparts. In a study by Campbell, they found that some "herbal" or "all natural" medications cost as low as $2.99 [7]. A second reason is the stigma associated with erectile dysfunction. In a French-sponsored study of 301 men, they found that even with a valid prescription for a PDE-5i, 12 % obtained their ED treatment via the Internet [16]. A third driver is that a patient can oftentimes obtain these medications without a prescription.

In one European study of 100 online pharmacies, 90.3 % did not require a prescription for prescription-only medications [17]. And in a Pfizer-sponsored study in the United Kingdom, 67 % of men purchased prescription-only erectile dysfunction medication over the Internet without a proper prescription [16].

With the high demand for erectile dysfunction medications, there has been a large increase in the sale of PDE5is and other supplements online. Currently, there are between 4500 and 15,000 websites that sell PDE5is and other substances used to treat ED, with some estimates up to 500,000. These websites receive 12.9 million visitors per month and sell approximately 2.3 million tablets per month [18]. Unfortunately, this leads to the huge potential for counterfeit PDE5is. It is believed that the majority of counterfeit PDE5is are thought to enter the market via the Internet [19]. Since this is an unregulated market, the FDA's Office of Enforcement and Import Operations has stated, "Consumers have little or no legal recourse if they experience a reaction to the unregulated medication or if they receive no therapeutic benefit at all. In addition to health risks, these pharmacies pose other risks to consumers, including credit card fraud, identity theft or computer viruses" [20]. There is also no recourse if the order is unfulfilled or if the wrong medication is sent. There is also no oversight or regulation into the quality or sanitary conditions of the manufacturing plant, the making of the drug, or the storage of the drug (Figs. 10.1, 10.2, and 10.3).

During the 5-year span from 2004 to 2008, 35.8 million counterfeit sildenafil tablets were seized in Europe. Only 10.1 % of samples labeled sildenafil 100 mg were within 10 % of advertised strength when analyzed with high-performance liquid chromatography. Many of the tablets consisted of talcum powder, commercial grade paints, Tylenol, metronidazole, and antiprotozoal ingredients. Many had large quantities of unidentified substances. In order to make the tablets blue, the counterfeiters have used blueprinter ink [21] (Fig. 10.4). In the Netherlands, the Dutch National Institute for Public Health and Environment examined 370 samples of PDE5i

Fig. 10.1 A Pfizer manufacturing facility. It is highly inspected and regulated and uses pure ingredients with stringent quality control. (Used with permission. Copyright © Pfizer Inc, New York, NY. All Rights Reserved)

Fig. 10.2 An unsanitary counterfeit factory in Ecuador that had been home to a counterfeit drug ring. (Used with permission. Copyright © Pfizer Inc, New York, NY. All Rights Reserved)

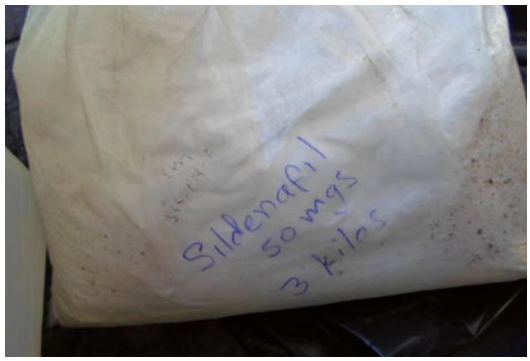

Fig. 10.3 An unsanitary bag used to store counterfeit Viagra® during the counterfeit manufacturing process. (Used with permission. Copyright © Pfizer Inc, New York, NY. All Rights Reserved)

Fig. 10.4 A bucket used to mix counterfeit Viagra®. Dangerous substances may be used by counterfeiters to make fake tablets appearing to be authentic medicine. For example, blue paint here is being used to make tablets of counterfeit Viagra®. (Used with permission. Copyright © Pfizer Inc, New York, NY. All Rights Reserved)

medications not obtained from a physician from 2000 to 2004. They discovered that only 10 out of the 370 were genuine. If the valid PDE5i was found, it was in lower concentrations than advertised. They also found that these products contained amphetamine, clomiphene, chloramphenicol, dipyrone, fluoxetine, tadalafil, yohimbine, gamma-amino butyric acid, caffeine, L-arginine, indigotin, and quinine [22].

In the United States, we have a similar problem. The president of America's Watchdog, a consumer advocacy group, has stated that 90% of all medicines sold over the Internet are fake [23]. The United States National Association of State Boards of Pharmacy was able to purchase several medications without prescriptions, including tadalafil, from 13 websites selling prescription-only medication; and they found that there was wide variation in the amount of active ingredient present, from none to far exceeding the level allowed. They also noted the medications did not comply with the drug manufacturer US standards due to inconsistencies in the amount of active ingredient and contamination [24].

Clearly, there is a huge potential for danger in this market. When looking at these counterfeit medications, there are multiple risks that are readily apparent. The most obvious risk is that there can be unknown potentially harmful phar-

maceutically active ingredients such as amphetamines. Additionally, there can be many dangerous chemicals such as paint, heavy metals, and printer ink. There also can be large variations in the dosage of the medication, which can lead to adverse side effects. In addition, since the physician can be bypassed, there is no one to review the possible drug-drug interactions of these products with the patient's own medications. One example of this would be a patient who is currently taking nitrates for angina who purchases sildenafil online. It has also been shown that if the online version does work, patients will think the prescription version will not work either and will not seek out further medical care [25].

Common Alternative Medications Used to Treat ED

Despite these dangers, we know that men continue to seek online treatments. However, trade-named pharmaceuticals such as PDE5is are not the only drugs available online. Patients often will seek "natural" or "herbal" supplements to treat their ED. Many of these supplements can also be found in health food stores, grocery stores, or convenience stores. The next section in this chapter will discuss several of the common supplements used to treat ED. Unfortunately, as with many herbal remedies, there are not many studies available for comprehensive review. Most studies are unblinded; many are underpowered, have limited follow-up, and do not use standardized questionnaires. This calls into question their results. Nonetheless, a summary of common alternative medications can be found in Table 10.1.

Ginseng

Ginseng cultivated in Korea is classified into three types, depending on how it is processed: fresh ginseng (<4 years old), white ginseng (4–6 years old and dried after peeling), and red ginseng (harvested when 6 years old, steamed, and dried) [26]. It is believed that red ginseng is the version found to be effective in the treatment of ED.

Ginseng is believed to work via the nitric oxide pathway. Ginsenosides, which are thought to be the principle active constituents of red ginseng, have been shown to cause a dose-dependent relaxation of the corpus cavernosal smooth muscle in rabbits by increasing release of nitric oxide which acts on the cGMP pathway [27].

It has been shown red ginseng to be superior to placebo in regard to improvement in ED [28–31]. Red ginseng has been shown to be more effective than placebo in treating psychogenic ED [28]. In three separate studies looking at patients with any kind of ED, they found that red ginseng did improve erections compared to placebo [29–31]. In a single study looking at mild vasculogenic ED, the researchers found no statistically significant improvement in the efficacy of red ginseng compared to placebo [32]. More studies are needed to fully evaluate this product.

Horny Goat Weed

This substance comes from the plant *Epimedium grandiflorum*, which is more commonly known as Horny goat weed. Its name comes from the story of a goat herder who noticed that goat has increased sexual desire after eating the plant [33]. The metabolically active ingredient in the plant is icariin.

There have been multiple suggested mechanisms of action. It has been shown to enhance eNOS expression and NO production in human endothelial cells [34], inhibit PDE5 in cavernosal smooth muscle cells [35], and have a positive effect on nitrergic nerves [36]. However, the active ingredients are found to have low oral bioavailability, poor absorption, and a short plasma half-life [37]. Researchers are currently in the process of developing a liposomal encapsulated formation to overcome these limitations [38].

Currently, there are no human studies regarding efficacy. There are a few case reports in which patients developed new onset tachyarrhythmia and hypomanic symptoms (sexual and verbal

Table 10.1 Summary of common alternative medications

Drug	Mechanism of action	Pharmacokinetics	Dosage	Side effects	Efficacy
Ginseng	Increases NO release	Unknown	600–1000 mg TID, no optimized dose	Insomnia, anxiety, hypomania, headache, diarrhea	More effective at treating psychogenic "all-cause" ED
Horny goat weed	PDE-5 inhibitor, increases NO release	Low oral bioavailability, poor absorption, and short plasma half-life	Unknown	Tachycardia, hypomania	No human studies
Yohimbine	Alpha-2 adrenoceptor antagonist, increases NO release	Rapidly absorbed, maximum plasma concentration <1 h, low bioavailability	Unknown	Increase in high blood pressure, increased heart rate, manic reactions, bronchospasm, palpitations, insomnia, anxiety, irritability, shivering, sweating	AUA recommends against its use for ED
Maca root	Unknown	Unknown	Unknown	Altered menstrual cycles, moodiness, cramps, gastritis, insomnia, synergistic with MAOi	Minimal human data
Ginkgo biloba	Increase NO bioavailability	Well absorbed	40–120 mg BID, no optimized dose	Increased bleeding risk, convulsions, potential carcinogen, GI	No significant benefit
Ptychopetalum olacoides	Unknown	Unknown	Unknown	Insomnia	Limited data. Could potentially increase libido
L-Carnitine	Unknown	Unknown	2 g per day, no optimized dose	Diarrhea, body odor, rash, and increase risk of seizures in patients with seizure history	Limited data
L-Arginine	Precursor molecule for NO	Extensive presystemic elimination by intestinal bacteria and intestinal and hepatic arginase activity that converts L-arginine to ornithine and urea	5 g per day, no optimized dose	Vomiting, diarrhea, flushing, arrhythmia, numbness	Very few studies, no increase in objective measurements
L-Citrulline	Converted to L-arginine in kidneys, precursor molecule to NO	Unknown	1.5 g per day, no optimized dose	Similar to L-arginine	Limited data

inappropriate behavior, irritable mood, hyperverbal speech) that required electro-cardioversion and antipsychotic medication for treatment [39].

Yohimbine

Yohimbine is a naturally occurring tryptamine alkaloid, which comes from the bark of African and Asian plants such as *Pausinystalia johimbe* and the root of *Rauvolfia serpentina.* It has been used in the past for erectile dysfunction, enhancing sexual performance, weight loss, and body building.

It has a high affinity for antagonizing alpha-2 adrenoceptors at the level of the locus coeruleus. This is believed to cause an increase in sexual desire. In the periphery it has been suggested that it blocks both the alpha-1 and alpha-2 adrenoceptors as well as enhancing the release of NO from cavernosal endothelial cells [40–42]. However, the true mechanism of action is not fully understood. It is rapidly absorbed, and the maximum plasma concentration is achieved in less than 1 h after oral administration [43]. The mean bioavailability is low and is subject to very high variation between individuals. It has been shown that the plasma concentration of it does not appear to be correlated with the dose of the compound administered [44].

After reviewing 15 years of meta-analyzed data, the AUA guidelines panel does not recommend yohimbine as a treatment for ED [45]. However, it may be somewhat effective in the treatment of delayed ejaculation [46]. Yohimbine may also have a role in the treatment of psychogenic ED. In a statement by the International Society for Sexual Medicine Standards committee, "If yohimbine has any potential indications for use in ED management, it would be among non-organic ED; apart from ED, yohimbine has shown a limited efficacy in the treatment of premature ejaculation" [41].

Its use has been associated with causing an increase in high blood pressure, increased heart rate, manic reactions, bronchospasm, palpitations, insomnia, anxiety, irritability, shivering, sweating, nausea, flushing, and headache [47]. People should not combine yohimbine with monoamine oxidase (MAO) inhibitors as effects may be additive. It should be used with caution when taken with medicines for HBP, tricyclic antidepressants, or phenothiazines. People with kidney problems or psychiatric conditions should not use yohimbe [48].

Maca Root (*Lepidium Meyenii*)

Maca root is a Peruvian plant found in central Andes used by native Andean populations as an aphrodisiac, energizer, and enhancer of fertility and sexual function [49]. The main ingredient is considered to be benzyl glucosinolates and polyphenols, (1R,3S)-1-methyl-1,2,3,4 tetrahydro-b-carboline-3-carboxylic acid (MTCA), and p-methoxybenzyl isothiocyanate among many other chemicals [50].

There are very minimal human data. However, in animal studies it has been shown to increase sexual behavior in male rats and mice and decreased latency to erection in testes-removed rats following oral administration [51]. Two human studies have shown significant positive effects of maca on sexual dysfunction or sexual desire in healthy postmenopausal women or healthy men [52, 53]. However, another study showed no effect on sexual function in healthy cyclists [54], and in another study, maca was insufficient in treating sexual dysfunction in the elderly [55]. In a double-blind clinical trial on 50 Caucasian men affected by ED, men were randomized to treatment with 2400 mg of maca dry extract or placebo. It was found that after 12 weeks, both those on maca and those with placebo had significant increases in IIEF score. However, those taking maca did have a larger increase in their IIEF score compared to placebo, and this increase was statistically significant. There was a 10 % improvement on "subjective" perception of general and sexual well-being in adult patients with ED who took maca while in the study [56].

The major side effects noted while taking this herbal supplement were found to be altered menstrual cycles, moodiness, cramps, gastritis, insomnia, and increase in "craving behavior."

[57] It does have a potential interaction with MAO enzyme. One of the chemicals found in the product, MCTA, has potential for mutagenic properties, and the French Agency for Sanitary and Security has warned consumers about this product in the past [58].

Ginkgo biloba

Ginkgo biloba is a living tree, belonging to Ginkgoaceae family, typically grown in China. Its extracts contain flavonoid glycosides and terpenoids, traditionally used for memory enhancement and blood flow improvement.

The most commonly used *Ginkgo biloba* extract is EGb761, which contains flavonoid glycosides, composed of kaempferol, quercetin, glucohamoside, esters, and terpenes of ginkgolides and bilobalides. It is believed to increase NO bioavailability, which may directly induce smooth muscle cell relaxation [59]. However, the full mechanism of action is not yet understood. It is well absorbed by humans after oral administration. However, since it is a mixture of substances, it is not possible to accurately determine pharmacokinetics [60].

In two randomized placebo-controlled trials, there was found to be no significant benefit on sexual function with ginkgo extracts [61, 62].

The National Toxicology Program has shown oral administration of ginkgo extract caused thyroid and liver cancer, atrophy of olfactory epithelium, nephropathy, and mononuclear cell lymphoma in mice [63]. One of the components, Quercetin, is a known mutagen [64]. In some human studies, no serious side effects were reported in clinical trials and side effects were similar to placebo [65]. However, it has been suggested that it can affect platelet aggregation and cause increased bleeding risk [66]. Some extracts of ginkgo contain 4′-O-methylpyridoxine which is a known neurotoxin; causes epileptic convulsions, vomiting, unconsciousness, and irritability; and can be fatal [67].

Ginkgo can interact with other medications. It decreases the effects of alprazolam, citalopram, and diazepam, while increasing the effects of clozapine, methadone, olanzapine, and fluvoxamine. There have been case reports of it causing hypomania if combined with St. John's wort, fluoxetine, and melatonin [65].

Ptychopetalum olacoides (Muira Puama)

Ptychopetalum olacoides is grown primarily in Brazil and it thought to improve sexual function in men. It also has been called "potency wood" [68]. Its mechanism of action is unknown, potentially related to dopaminergic, cholinergic, or adrenergic neurotransmitters.

In a single study, it was found that 60 % of men with low libido reported an increased sexual desire. It also found that 50 % of men with poor erection have reported improved erection function following administration [69]. It should be noted that there are very few studies evaluating this product, and the side effects are largely unknown. However, it could potentially cause insomnia.

L-Carnitine

L-Carnitine is a naturally occurring amino acid in the body. A single study has recommended propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day as a possible dose. Yet very few studies have evaluated the product. In one study it was shown to increase the peak systolic velocity, while decreasing end-diastolic velocity in the penis which leads to improved nocturnal penile tumescence. It also improved the IIEF-15 erectile function, orgasm, sexual desire, and general sexual well-being domain scores at 3 months. It was noted that when men no longer consumed the product, the improvements stopped [70].

If 5 g or more grams are taken per day, it may cause diarrhea. Other rare side effects include increased appetite, body odor, rash, and increase risk of seizures in those with a history of seizures. It also could potentially cause decreased effectiveness in individuals taking oral thyroid medication [71].

L-Arginine

L-Arginine is another naturally occurring amino acid. Its optimal dosage is unknown, but doses of 5 g/day have been recommended. It is the precursor of NO and has been shown to provide the substrate for the NO/cGMP/VEGF pathway. It is believed to cause vasodilation and penile smooth muscle relaxation [72]. Absorption is limited by extensive presystemic elimination by intestinal bacteria and intestinal and hepatic arginase activity that converts L-arginine to ornithine and urea [73].

There are few studies to evaluate true efficacy. In one study 50 patients with organic ED were randomized to receive placebo or 5 g L-arginine daily for 6 weeks. They found significant subjective improvement in 31 % of the men taking L-arginine and 12 % of the men taking placebo. However, it should be noted that the improvement was "subjective." Additionally, the study showed that the subjective improvement was not associated with hemodynamic changes in corpus cavernosum circulation as assessed by penile duplex ultrasonography. The lack of hemodynamic changes was attributed to insufficient intracavernosal concentration of L-arginine and/or the lack of delivery of L-arginine to the corpus cavernosum when administered orally [74]. In a second study that was a double-blind crossover study of 32 men, there was no benefit with 1500 mg of arginine given daily for 17 days [75].

Its potential side effects include vomiting, diarrhea, flushing, arrhythmia, and numbness.

L-Citrulline

L-Citrulline is another amino acid suggested as a treatment for ED. Optimal dosing is unknown. Oral L-citrulline escapes intestinal and liver metabolism, inhibits arginase activity, and is converted by the kidneys into L-arginine, thus providing plenty of substrate for the L-arginine/NO/cGMP/VEGF pathway [73].

One small study has shown a greater increase in a male's erectile hardness score compared to placebo. It also caused a greater increase in the mean number of intercourses compared to placebo. All patients reporting an erection hardness score improvement from 3 to 4 reported being very satisfied while taking the L-citrulline [76].

Side effects are similar to that of arginine.

Conclusion

ED is an extremely common condition, and many men seek treatment. Whether it is due to cost, embarrassment, availability, or ease of procurement, many men turn to the Internet to seek their treatment. Unfortunately, many, if not most, of the PDE5is purchased from online pharmacies are counterfeit with potentially harmful contaminants and/or ingredients. Many of these PDE5is can be ordered without a prescription eliminating the physician-patient interaction and the possibility of detecting other comorbid conditions associated with ED such as coronary artery disease. Also drug-drug interactions may be missed.

If men seek herbal therapies instead of more traditional therapies, most of what is available is ineffective. Of those that show effectiveness, the clinical trials demonstrating this are often unblinded and underpowered, have very limited follow-up, and do not use standardized questionnaires. Therefore, the results of these trials are questionable. At this time, the authors recommend more traditional approaches to the treatment of ED. Patients that seek treatments online should be warned of the potential harms.

References

1. Wilt T, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. JAMA. 1998;280:1604.
2. Blumenthal M, The American Botanical Council. The ABC, clinical guide to herbs. New York: Thieme; 2003. p. 383–5.
3. Kaptchuk T. Acupuncture: theory, efficacy and practice. Ann Intern Med. 2002;136:374.
4. Barnes P, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States. Adv Data. 2004;343:1–19.

5. Gutierrez S, Ang-Lee M, Walker D, Zacny J. Assessing subjective and psychomotor effects of the herbal medication valerian in healthy volunteers. Pharmacol Biochem Behav. 2004;78:57–64.
6. Goldman P. Herbal medicines today and the roots of modern pharmacology. Ann Intern Med. 2001;135:594.
7. Campbell N, Clark J, Stecher V, Thomas J, Callanan A, Donnelly B, Goldstein I, Kaminetsky J. Adulteration of purported herbal and natural sexual performance enhancement dietary supplements with synthetic phosphodiesterase type 5 inhibitors. J Sex Med. 2013;10:1842–9.
8. Newmaster S, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. DNA bar coding detects contamination and substitution in North American herbal products. BMC Med. 2013;11:222.
9. Stoeckle M, Gamble C, Kirpeka R, Young G, Ahmed S, Little D. Commercial teas highlight plant DNA barcode identification successes and obstacles. Sci Rep. 2011;1:42.
10. Baker D, Stevenson D, Little D. DNA barcode identification of black cohosh herbal dietary supplements. J AOAC Int. 2012;9:1023–34.
11. Etienne C. International Medical Products Anticounterfeiting Taskforce (IMPACT). Counterfeit Drugs Kill! World Health Organization; 2008.
12. Ko R. Adulterants in Asian patent medicines. N Engl J Med. 1998;339:847.
13. Hill H. Counterfeit medicines—how much of a risk to public health are they? Pharm J. 2005;275:520.
14. DHHS. Adverse event reporting for dietary supplements: an inadequate safety valve. US: office of the inspector general, HHS; 2001.
15. Marcus D, Grollman A. Botanical medicines—the need for new regulations. N Engl J Med. 2002;347:2073.
16. Cracking counterfeit: counterfeit medicines—the scope of the problem. Ireland: Pfizer; 2010.
17. Thompson J, Banks I. European Alliance for Access to Safe Medicines. The counterfeiting superhighway. Eur Alliance Access Safe Med. 2008:1–32.
18. Ukens C. Pharmacists can help stop counterfeit drugs. Drug Topics. 2004;148:31.
19. Dorsey P, Hellstrom W. The illicit sale of medications for the treatment of erectile dysfunction. Medscape Urol. 2007:1–8.
20. US Food and Drug Administration. FDA targets illegal online pharmacies in globally coordinated action. FDA News Release. 2014. Web.
21. Stecher V, Jackson G, Banks I, Arver S. Analysis of pharmaceuticals seized by authorities for suspicion of being counterfeit viagra (Sildenafil Citrate). Eur Soc Sexual Med. 2009:1.
22. Venhuis B, Barends D, Zwaagstra M, de Kaste D. Recent developments in counterfeits and imitations of viagra, Cialis and Levitra: a 2005–2006 update. RIVM Rep. 2007:1–55.
23. Megget K. The “global disaster” of fake internet pharmacies. pharmatechnologist.com. Web. 19 July 2007. Accessed 2 Mar 2015.
24. Catizone C. Counterfeit drugs and states’ efforts to combat the problem. J Pharm Pract. 2006;19:165–70.
25. Jackson G, Arver S, Banks I, Strecher V. Counterfeit PDE-5i pose significant safety risk. Int J Clin Pract. 2010;64:497–504.
26. Yun T. Panax ginseng—a non-organ-specific cancer preventive? Lancet Oncol. 2001;2:49–55.
27. Choi Y, Rha K, Choi H. In vitro and in vivo experimental effect of Korean red ginseng on erection. J Urol. 1999;162:1508–11.
28. Jang D, Lee M, Byung-Cheul S, Ernst E. Red ginseng for treating erectile dysfunction: a systematic review. Br J Clin Pharmacol. 2008;66:444–50.
29. Hong B, Ji Y, Hong J, Nam K, Ahn T. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. J Urology. 2002;168:2070–3.
30. Choi H, Choi Y, Kim J. Penile blood change after oral medication of Korean red ginseng in erectile dysfunction patients. J Ginseng Res. 2003;27:165–70.
31. de Andrade E, de Mesquita A, Claro Jde A, de Andrade P, Ortiz V, Paranhos M. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. Asian J Androl. 2007;9:241–4.
32. Kim S, Paick S. Clinical efficacy of Korean red ginseng on vasculogenic impotent patients. Korean J Androl. 1999;17:23–8.
33. Horny Goats Weed. Herb Wisdom. Hallnet Ltd, n.d. Accessed 1 Mar 2015.
34. Xu H, Huang Z. Icariin enhances endothelial nitric-oxide synthase expression on human endothelial cells in vitro. Vascul Pharmacol. 2007;47:18–24.
35. Ning H, Xin Z, Lin G, Banie L, Lue T, Lin C. Effects of icariin on phosphodiesterase-5 activity in vitro and cyclic guanosine monophosphate level in cavernous smooth muscle cells. Urology. 2006;68:1350–4.
36. Shindel A, Xin Z, Lin G, Fandel T, Huang Y, Banie L, Breyer B, Garcia M, Lin C, Lue T. Erectogenic and neurotrophic effects of icariin, a purified extract of horny goat weed (Epimedium spp.) in vitro and in vivo. J Sex Med. 2010;7:1518–28.
37. Ye L, Chen J, Liu S. Pharmacokinetics of icariin in rats. Chin Pharmaceut J. 1999;34:33–6.
38. Yang W, Yu X, Chen X, Zhang L, Lu C, Zhao Y. Pharmacokinetics and tissue distribution profile of icariin propylene glycol-liposome intraperitoneal injection in mice. J Pharm Pharmacol. 2012;64:190–8.
39. Partin J, Pushkin Y. Tachyarrhythmia and hypomania with horny goat weed. Psychosomatics. 2004;45:536–7.
40. Goldberg M, Roberston D. Yohimbine; a pharmacological probe for the study of the a2-adrenoreceptor. Pharmacol Rev. 1983;35:143–80.

41. Porst H, Burnett A, Brock G, Bhanem H, Giuliano F, Glina S, Hellstrom W, Martin-Morales A, Salonia A, Sharlip I. SOP conservative (medical and mechanical) treatment of erectile dysfunction. J Sex Med. 2013;10:130–71.
42. Simonsen U, Prieto D, Hernandez M, Saenz de Tejada I, Garcia-Sacristan A. Prejunctional alpha 2-adrenoceptors inhibit nitrergic neurotransmission in horse penile resistance arteries. J Urol. 1997;157:2356–60.
43. Owen J, Nakatsu S, Fenemore J, Condra M, Surridge D, Morales A. The pharmacokinetics of yohimbine in man. Eur J Clin Pharmacol. 1987;32:577–82.
44. Guthrie S, Hariharan M, Grunhaus L. Yohimbine bioavailability in humans. Eur J Clin Pharmacol. 1990;39:409–11.
45. Montague D, Barada J, Belker A, Levine L, Nadig P, Roehrborn C, Sharlip I, Bennett A. Clinical guidelines panel on erectile dysfunction: summary report on the treatment of organic erectile dysfunction. J Urol. 1996;156:11.
46. Adeniyi A, Brindley G, Pryor J, Ralph D. Yohimbine in the treatment of orgasmic dysfunction. Asian J Androl. 2007;9:403–7.
47. Efsa, ANS Panel (EFSA Panel on Food Additives and Nutrient Sources Added to Food). Scientific Opinion on the evaluation of the safety in use of Yohimbe (Pausinystalia yohimbe (K. Schum.) Pierre ex Beille). EFSA J. 2013;11:46.
48. National Center for Complementary and Alternative Medicine. Herbs at a glance: Yohimbe. United States department of health and human services. July 2012. Accessed March 2015.
49. Gonzales G. Ethnobiology and ethnopharmacology of Lepidium meyenii(Maca), a plant from the peruvian highlands. Evid Based Complement Alternat Med. 2012:1–10.
50. Clement C, Diazgrados D, Avula B, Kahn I, Mayer A, Aguirre D, Manrique I, Kruezer M. Influence of colour type and previous cultivation on secondary metabolites in hypocotyls and leaves of maca (Lepidium meyenii Walpers). J Sci Food Agric. 2010;90:861–9.
51. Zheng B. Effect of a lipidic extract from Lepidium meyenii on sexual behavior in mice and rats. Urology. 2000;55:598–602.
52. Brooks N, Wilcox G, Walker K, Ashton J, Cox M, Stojanovska L. Beneficial effects of Lepidium meyenii (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. Menopause. 2008;15:1157–62.
53. Gonzales G, Cordova A, Vega K, Chung A, Villena A, Gonez C, Castillo S. Effect of Lepidium meyenii (MACA) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. Andrologia. 2002;34:367–72.
54. Stone M, Ibarra A, Roller M, Zangara A, Stevenson E. A pilot investigation into the effect of maca supplementation on physical activity and sexual desire in sportsmen. J Ethnopharmacol. 2009;126:574–6.
55. Ernst E, Posadzki P, Lee M. Complementary and alternative medicine (CAM) for sexual dysfunction and erectile dysfunction in older men and women: an overview of systematic reviews. Maturitas. 2011;70:37–41.
56. Zenico T, Cicero A, Valmorri L, Mercuriali M, Bercovich E. Subjective effects of Lepidium meyenii extract on well-being and sexual performances in patients with mild erectile dysfunction: a randomised, double-blind clinical trial. Andrologia. 2009;41:95–9.
57. Piacente S, Carbone V, Plaza A, Zampelli A, Pizza C. Investigation of the tuber constituents of maca (Lepidium meyenii Walp). J Agric Food Chem. 2002;50:5621–5.
58. APSSA. From the French Agency of Sanitary Security on foods relative to the risk assessment for health by consuming pulverized maca roots or as alimentary supplement. AfssaSaisine 2004-SA-0155 2004:1–3.
59. Schmitt C, Dirsch V. Modulation of endothelial nitric oxide by plant-derived products. Nitric Oxide. 2009;21:77–91.
60. Ude C, Schubert-Zsilavecz M, Wurglics M. Ginkgo biloba extracts: a review of the pharmacokinetics of the active ingredients. Clin Pharmacokinet. 2013;52:727–49.
61. Kang B, Lee S, Kim M, Cho M. A placebo controlled, double-blind trial of Ginkgo biloba for antidepressant-induced sexual dysfunction. Hum Psychopharmacol. 2002;17:279–84.
62. Wheatley D. Triple-blind, placebo-controlled trial of Gingko biloba in sexual dysfunction due to antidepressant drugs. Hum Psychopharmacol. 2004;19:545–8.
63. National Institutes of Health. Ntp technical report on the toxicology and carcinogenesis studies of Ginkgo biloba (cas no. 90045-36-6) in f344/n rats and b6c3f1/n mice(gavage studies). NIH Publication No. 13-5920. 2013:184.
64. Hardigree A, Epler J. Comparative mutagenesis of plant flavonoids in microbial systems. Mutat Res. 1978;58:231–9.
65. Birks J, Grimley E, Van Dongen M. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2002;4. Article ID CD003120.
66. Fugh-Berman A. Herb-drug interactions. Lancet. 2000;355:134–8.
67. Leistner E, Drewke C. Ginkgo biloba and ginkgotoxin. J Nat Prod. 2010;73:86–92.
68. Shamloul R. Natural aphrodisiacs. J Sex Med. 2010;7:39–49.
69. Waynberg J. Yohimbine vs. muira puama in the treatment of sexual dysfunction. Am J Nat Med. 1994;1:8–9.
70. Cavallini G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. Urology. 2004;62:641–6.

71. University of Maryland Medical Center. Carnitine (L-Carnitine). University of Maryland Medical Center (UMMC). March 2011. Accessed March 2015.
72. Komori K, Tsujimura A, Takao T, Matsuoka Y, Miyagawa Y, Takada S, Honomura N, Okuyama A. Nitric oxide synthesis leads to vascular endothelial growth factor synthesis via the NO/cyclic guanosine 3′,5′-monophosphate (cGMP) pathway in human corpus cavernosal smooth muscle cells. J Sex Med. 2008;5:1623–35.
73. Morris Jr S. Enzymes of arginine metabolism. J Nutr. 2004;134:2743S–7.
74. Chen J, Wollman Y, Chernichovsky T, Iaina A, Sofer M, Matzkin H. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. BJU Int. 1999;83:269–73.
75. Klotz T, Mathers M, Braun M, Bloch W, Engelmann U. Effective of oral L-arginine in first line treatment of erectile dysfunction in a controlled crossover study. Urol Int. 1999;62:220–3.
76. Cormio L. Oral L-citrulline supplementation improves erection hardness in men with mild erectile dysfunction. Urology. 2011;77:119–22.

Prescription Medications that Affect Sexual Function

11

Michelle Herberts and Kevin T. McVary

Physiologic Control of Erection and Male Sexual Function

It is necessary to establish a basic understanding of normal sexual function prior to discussion of potential mechanisms for drug-induced pathology. Normal male sexual function requires (1) an intact libido, (2) the ability to achieve and maintain penile erection, (3) ejaculation, and (4) detumescence [1, 2]. The major anatomic structures of the penis that are involved in erectile function include the paired corpora cavernosa and the single corpus spongiosum that encloses the urethra. The tunica albuginea, a collagenous sheath, individually surrounds each corpus. The microarchitecture of the corpora is composed of a mass of smooth muscle which contains a network of endothelial-lined lacunar spaces. Penile tumescence leading to erection depends on the increased flow of blood into the lacunar network after complete relaxation of the arteries and corporal smooth muscle. Subsequent compression of the trabecular smooth muscle against the fibroelastic tunica albuginea causes a passive closure of the emissary veins and accumulation of blood in the corpora. In the presence of a full erection and a competent valve mechanism, the corpora become noncompressible cylinders from which blood cannot escape.

The central nervous system exerts an important influence by either stimulating or antagonizing spinal pathways that mediate erectile function and ejaculation. These interactions are mediated by a combination of central and peripheral innervation [1]. Sensory nerves that originate from receptors in the penile skin and glans converge to form the dorsal nerve of the penis, which travels to the S2-S4 dorsal root ganglia via the pudendal nerve. Parasympathetic nerve fibers to the penis arise from neurons in the intermediolateral columns of S2-S4 sacral spinal segments. Sympathetic innervation originates from the T-11 to the L-2 spinal segments and descends through the hypogastric plexus. Neural input to smooth muscle tone is crucial to the initiation and maintenance of an erection. There is also an intricate interaction between the corporal smooth muscle cell and its overlying endothelial cell lining (Fig. 11.1).

Nitric oxide, which induces vascular relaxation, promotes erection and is opposed by endothelin-1 (ET-1), which mediates vascular contraction (Fig. 11.1). Nitric oxide is synthe-

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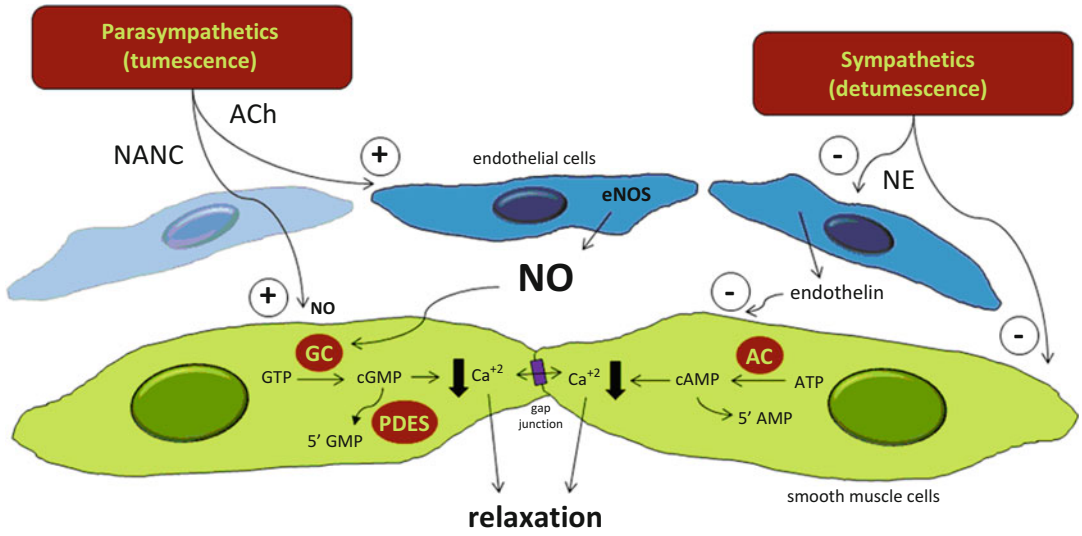

Fig. 11.1 Molecular mechanisms mediating erectile function. *ACh* acetylcholine, *eNOS* endothelial nitric oxide synthase, *GC* guanylyl cyclase, *NANC* nonadrenergic noncholinergic, *NE* norepinephrine, *NO* nitric oxide, *PDE-5* type-5 phosphodiesterase

sized from L-arginine by nitric oxide synthase (NOS) and is released from the nonadrenergic, noncholinergic (NANC) autonomic nerve supply to act post-junctionally on smooth muscle cells. Nitric oxide increases the production of cyclic 3′,5′-guanosine monophosphate (cyclic GMP), which interacts with protein kinase G and decreases intracellular calcium, causing relaxation of the smooth muscle. Cyclic GMP is gradually broken down by phosphodiesterase type 5 (PDE-5). Inhibitors of PDE-5, such as the oral medication sildenafil, maintain erections by reducing the breakdown of cyclic GMP. However, if nitric oxide is not produced at a basal level, the addition of PDE-5 inhibitor is not effective, as the drug facilitates but does not initiate the initial enzyme cascade. In addition to nitric oxide, vasoactive prostaglandins (PGE_1, $PGF_{2\alpha}$) are synthesized within the cavernosal tissue and increase cyclic AMP levels, also leading to relaxation of cavernosal smooth muscle cells.

Ejaculation is stimulated by the sympathetic nervous system, which results in contraction of the epididymis, vas deferens, seminal vesicles, and prostate, causing seminal fluid to enter the urethra. Seminal fluid emission is followed by rhythmic contractions of the bulbocavernosus and ischiocavernosus muscles, leading to ejaculation. Detumescence is mediated by norepinephrine released from the sympathetic nerves, release of ET-1 from the vascular surface, and contraction of smooth muscle induced by activation of postsynaptic α-adrenergic receptors [1]. These events increase venous outflow and restore the flaccid state. Venous leak can cause premature detumescence and is thought to be caused by insufficient relaxation of the corporal smooth muscle.

Erectile dysfunction (ED) may result from three basic mechanisms: (1) failure to initiate (psychogenic, endocrinologic, or neurogenic), (2) failure to fill (arteriogenic), and (3) failure to store (venoocclusive dysfunction) adequate blood volume within the lacunar network. The inability to initiate an erection may have psychogenic, vasculogenic, endocrinologic, or neurogenic etiologies. These categories are not mutually exclusive, and multiple factors contribute to ED in many patients. ED has also been commonly associated with prescription and nonprescription medications. The remainder of this chapter will focus on the literature and the hypothesized mechanisms of dysfunction surrounding this relatively common clinical entity.

Drug-Induced Sexual Dysfunction and Its Mechanisms (Fig. 11.2)

Medication-induced ED is estimated to occur in 25 % of men seen in general medical outpatient clinics [3]. The adverse effects related to drug therapy are additive, especially in older men. In this section we review the existing literature on this subject. It is important to remember that virtually all data (with a few exceptions) are largely subjective reports based on empiric observation, case series, physician and patient surveys, and pre- and post-marketing drug trials [4]. With all of the unvalidated information that exists regarding this subject, it is especially important for physicians to be aware of the disease process being treated and give strong consideration to whether or not the disease pathophysiology itself is contributing to the sexual dysfunction [4]. In addition, physicians should pay particular attention to the presence of other risk factors for ED (i.e., the patient's psychosocial status, age, weight, educational level) which exist outside of the disease being treated and the drug in question [5]. One section of this chapter addresses management strategies for the treatment of drug-induced sexual dysfunction.

Antihypertensive Agents

The most frequent organic cause of ED is a disturbance of blood flow to and from the penis. Atherosclerotic or traumatic arterial disease can decrease flow to the lacunar spaces, resulting in decreased rigidity and an increased time to full erection. In theory, any agent that decreases systemic pressure, subsequently altering the hemodynamics of pelvic blood flow, can potentiate ED [1]. Thus, it is not surprising that sexual dysfunction has been associated with nearly all available classes of hypertensive medication [4] (Table 11.1). These agents have been strongly correlated with new onset ED. While hypertension alone is considered a risk factor for ED, a population-based prospective study of over 1000 randomly selected men in the Massachusetts Male Aging Study (MMAS) identified select antihypertensive treatments (specifically thiazide diuretics, spironolactone,

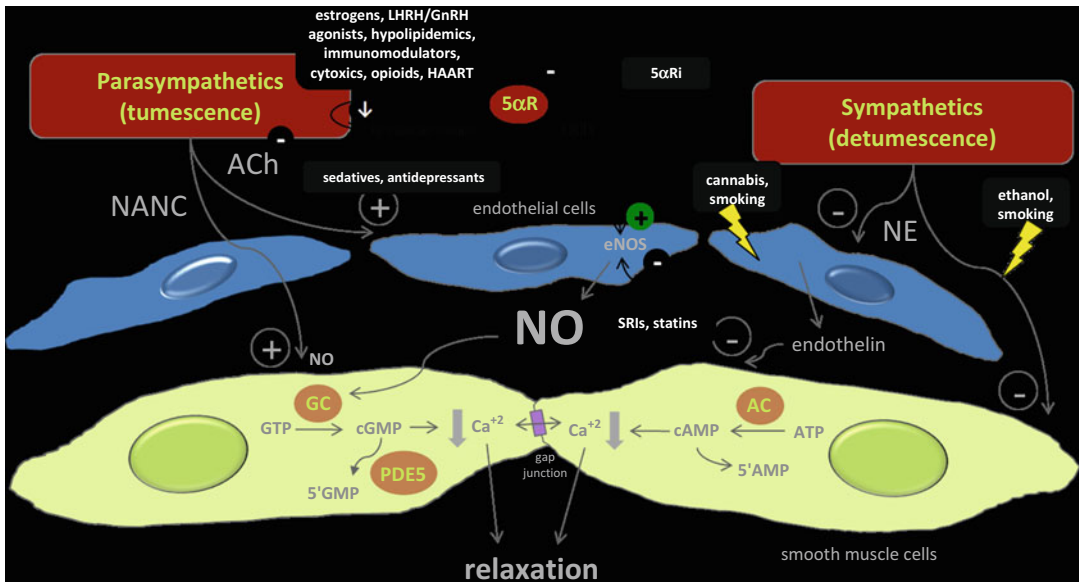

Fig. 11.2 Proposed mechanisms of drug-induced erectile dysfunction. *5αR* 5-alpha reductase, *5αRi* 5-alpha reductase inhibitor, *ACh* acetylcholine, *eNOS* endothelial nitric oxide synthase, *GC* guanylyl cyclase, *HAART* highly active antiretroviral therapy, *NANC* nonadrenergic noncholinergic, *NE* norepinephrine, *NO* nitric oxide, *PDE-5* type-5 phosphodiesterase, *SSRI* selective serotonin reuptake inhibitor

Table 11.1 Hypothesized mechanisms of drug-induced sexual dysfunction

	Drug class	Hypothesized mechanism of sexual dysfunction
Antihypertensives	β-Blockers	• Decreased corporal blood flow • Suppression of CNS sympathetic outflow • Inhibition of β2-mediated peripheral vasodilation
	Thiazide diuretics	• Decreased corporal blood flow
	Sympatholytics (methyldopa, clonidine)	• Stimulation of α_2-adrenergic receptors in the hypothalamus
	Calcium-channel blockers	• Decreased corporal blood flow via altered calcium flux in penile smooth muscle cells
	α-Blockers	• Relaxation of the seminal vesicles leading to absence of ejaculation
Psychotropics	Neuroleptics	• Decreased dopaminergic-enhanced libido • Stimulation of prolactin release from the hypothalamus • Antagonism of α_1-adrenergic receptors leading to ejaculatory dysfunction and priapism
	Antidepressants (tricyclics, SSRIs)	• Anticholinergic activity • Stimulation of prolactin release from the hypothalamus • Decreased dopaminergic-enhanced libido • Sympathomimetic activity • Alteration of nitric oxide synthesis (SSRIs) • 5HT2C receptor activation and delay in ejaculatory reflex arc
	Anxiolytics/tranquilizers	• Centrally mediated sedation • Anticholinergic activity • Decreased dopaminergic-enhanced libido • Stimulation of prolactin release from the hypothalamus
Hormone mediators	Estrogens, GnRH agonists, LHRH agonists	• Suppression of gonadotropin production
	H_2 blockers	• Stimulation of prolactin release from the hypothalamus • Competition with native testosterone for androgen receptor binding
	5α-Reductase inhibitors	• Decreased nitric oxide synthase activity • Prostatic acinar apoptosis
	HIV therapy (protease inhibitors)	• Increased aromatization of testosterone
Hypolipidemics	Fibrates (i.e., clofibrate, gemfibrozil)	• Decreased steroidogenesis • Decreased nitric oxide synthase activity (statins)
	Statins (i.e., pravastatin)	
Miscellaneous	Digoxin	• Decreased corporal blood flow via altered calcium flux in penile smooth muscle cells
	Cytotoxic agents (methotrexate, thalidomide)	• Destruction of gonadal tissue
	Immunomodulators (interferon, target of rapamycin inhibitors)	• Decreased testosterone levels
Toxins/recreational drugs	Cigarette smoking	• Decreased nitric oxide bioavailability • Ultrastructural damage to the vascular endothelium and peripheral nerves
	Ethanol	• Decreased nitric oxide bioavailability • Ultrastructural damage to the peripheral nerves • Impairment of hepatic estrogen metabolism • Destruction of gonadal tissue
	Opioids	• Decreased testosterone levels
	Cannabis	• Ultrastructural damage to the vascular endothelium

β-blockers, methyldopa, and clonidine), and not the condition itself, as an independent risk factor [6]. However, logistic regression analyses with adjustment for comorbidities and health behaviors attenuated these associations, finding that only nonthiazide diuretics and benzodiazepines were associated with ED to statistical significance. Studies like these make it difficult to interpret the previous literature surrounding antihypertensive-induced ED.

Among the antihypertensive agents, the β-blockers have been one of the most commonly implicated classes. The prevalence of β-blocker-induced sexual dysfunction has been reported to be anywhere from 5 to 43 % [7]. This number is under much debate recently, however, due to some claims that sexual dysfunction caused by β-blockers may be in part due to the healthcare provider mentioning such side effects at the time of initial prescribing [8]. ED has been reported with higher doses of propranolol [4] as well as with other, newer β-blockers as well [4, 7]. The proposed pathophysiology is via decreased corporal blood flow, suppression of CNS sympathetic outflow, and, in the case of nonspecific blockers, inhibition of β2-mediated peripheral vasodilation leading to insufficient relaxation of the corpora [4, 7]. Atenolol, a β-1-selective antagonist, has also been reported to decrease the levels of circulating testosterone in men. In cases where a β-1-selective antagonist may be used, nebivolol may be appropriate as it has been shown to have nitric oxide potentiating effects, thus leading to vasodilation and an improvement in erectile function [9].

Thiazide diuretics are some of the most commonly used antihypertensives. This class is also commonly implicated as eliciting ED. The incidence of thiazide diuretic-induced ED has been reported to be anywhere from 4 to 32 % [7]. It is hypothesized that sexual dysfunction may occur due to impairment of neural input into the areas of the hypothalamus that control male sexual function. Also of note, sexual dysfunction related to thiazide diuretics seems to greatly improve with lifestyle modifications and weight reduction [9]. Calcium channel blockers and vasodilators such as hydralazine are other antihypertensive agents linked to drug-induced ED. While the mechanism of action is not completely understood, it has been hypothesized that these drugs act directly at the corporal level (for instance, calcium channel blockers) or indirectly by reducing pelvic blood pressure, which is important in the development of penile rigidity.

Antihypertensive classes such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may be considered alternative medications for drug-induced erectile dysfunction caused by other antihypertensive medications. It has been reported that ACE inhibitors have a neutral effect on sexual function in men while the ARBs actually exhibit a positive effect on erectile function in multiple studies. The mechanism for this benefit is currently unknown and more studies will be needed in order to further investigate these findings [10]. If this is not an option, PDE-5 inhibitors may be added to a current medication regimen if contraindications such as nitrates have not been prescribed [11].

While α-blockers have historically been used for hypertension, the practicing urologist is often more familiar with the use of this class of drugs in the treatment of benign prostatic hyperplasia (BPH). Epidemiologic evidence suggests that ED and BPH are conditions that often arise together. Because clinical data suggest that addition of an α1-blocker to a PDE-5 inhibitor can actually attenuate ED, multiple groups have investigated the effects of concomitant application of various α1-blocker and PDE-5 inhibitor combinations on human [12] and animal [13] cavernosal tissue as compared to each drug alone. Recent studies have shown that the combination of α1-blocker and PDE-5 inhibitors resulted in improvement of the IIEF score by 3.6 points when compared to α1-blockers alone. Interestingly, the combination of PDE-5 inhibitors with α1-blocker medications was also shown to increase urinary flow rates by 1 ml/s when compared to monotherapy with α1-blockers [12]. Animal studies suggest that α1-blockers can actually increase NO synthesis in rats, therefore altering sympathetic tone and increasing blood flow in penile tissue when bladder outlet obstruction and ED are present [13].

Psychotropic Medications

Psychotropic agents—particularly neuroleptics, tricyclics, and selective serotonin reuptake inhibitors (SSRIs)—are associated with erectile, ejaculatory, orgasmic, and sexual desire difficulties (Table 11.1). Mental illness and the management of mental disorders are a significant cause of sexual dysfunction in men. A recent population study reported a fivefold increase in odds of self-reported complete ED among men who used selected antidepressant therapy (principally selective serotonin reuptake inhibitors and tricyclics) which exceeded the risk of ED attributed to depression symptoms or diagnosis [6]. Antidepressant-associated ED is reported to occur with prevalence rates from 30 to 90 % [14, 15]. Worsening or initiation of sexual dysfunction has been reported with agents for all antidepressant classes including monoamine oxidase inhibitors, tricyclic antidepressants, and SSRIs. Among the SSRIs, paroxetine and escitalopram have been associated with the highest risk of sexual dysfunction [16]. Bupropion, nefazodone, and mirtazapine appear less likely to cause sexual dysfunction [14]. A number of molecular pathways have been implicated in antidepressant-induced sexual adverse events. Serotonin has been hypothesized to inhibit normal sexual response by decreasing dopamine-enhanced libido, arousal, and erection and increasing prolactin release from the hypothalamus [15]. SSRIs have also been shown to be potent inhibitors of nitric oxide synthesis [17].

Given the high prevalence of antidepressant-induced sexual dysfunction, a prospective, parallel group, randomized, double-blind, placebo-controlled trial was undertaken to evaluate the safety and efficacy of PDE-5 inhibitors in the treatment of this disorder [18–20]. Ninety male outpatients at three different university medical centers with major depression in remission and sexual dysfunction associated with either selective or nonselective SSRI antidepressant treatment were randomly assigned to take sildenafil at a flexible dose (50–100 mg) for 6 weeks. Multiple different validated and unvalidated questionnaires were administered, including the IIEF [18]. Based on several analyses, the authors concluded that sildenafil was well tolerated and significantly improved erectile function and overall sexual satisfaction in men with SSRI-associated ED [18–20]. These data provide level 1 evidence that a PDE-5 inhibitor may be successfully used to treat SSRI-associated ED without interruption of antidepressant therapy.

Antipsychotic medications are associated with both erectile and ejaculatory dysfunction in up to 50 % of patients [7]. Dopamine is considered a key target of neuroleptic medications and is known to have multiple effects in the central nervous system. It is well established that dopamine inhibits prolactin release. Decreases in dopamine action thus lead to hyperprolactinemia. Increased serum levels of prolactin may decrease libido by suppressing gonadotropin-releasing hormone (GnRH), therefore decreasing testosterone levels, resulting in decreased libido, anorgasmia, and ED. If deemed necessary, a PDE-5 inhibitor may be added or alternative options such as aripiprazole, a prolactin-sparing atypical antipsychotic, may be used. Aripiprazole has been shown to reduce sexual dysfunction in patients who had this side effect from other medications [21]. In addition, many drugs that produce central nervous system sedation or depression, such as anxiolytics and tranquilizers, are also thought to lead to ED potentially via CNS anti-dopaminergic effects and increased prolactin release [1].

CNS sedatives are also known to have residual anticholinergic effects. While acetylcholine plays a significant role in normal erectile function, the use of anticholinergic agents has not been associated with ED as frequently as one might expect [4]. ED has, however, been reported with the anticholinergic anti-arrhythmic drug disopyramide. In addition, many of the antidepressants, namely, tricyclics and select SSRIs, maintain residual anticholinergic properties. It is possible that the sexual dysfunction from these medications is mediated in part by their anticholinergic properties.

Hormonal Agents

Androgens are known to increase libido, but their exact role in erectile function remains unclear [1]. Normal levels of testosterone appear to be important for erectile function, particularly in older males. It has been shown that androgen replacement therapy can improve depressed erectile function when ED is secondary to hypogonadism. As such, it is not surprising that any drug that interferes with testosterone production or action might lead to sexual dysfunction (Table 11.1). Estrogens, GnRH agonists, LHRH agonists, and corticosteroids can cause ED by suppressing gonadotropin production. Certain drugs like spironolactone, cyproterone acetate, ketoconazole, aminoglutethimide, and other similar drugs have also been shown to have antiandrogen activity and have each been linked to drug-induced sexual dysfunction [1, 4, 7]. These agents often resemble the molecular structure of testosterone and compete with native testosterone for binding to androgen receptors; they have also been shown to induce hyperprolactinemia. Multiple reports have linked H_2 blockers to sexual dysfunction. Ranitidine and cimetidine have both been shown to increase prolactin levels and act as antiandrogens [1, 4].

5α-Reductase Inhibitors

The potential sexual side effects, including ED, decreased libido and ejaculatory problems, which have been reported with 5α-reductase inhibitors (dutasteride and finasteride) are of particular relevance to the urology patient. These drugs block the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT). Animal models have demonstrated decreased NOS activity with decreased DHT, and thus, it has been proposed that 5α-reductase inhibitors elicit sexual dysfunction by indirectly attenuating nitric oxide synthase activity [22]. ED with these medications has also been thought to be due to the decrease in androgens leading to decrease in structural integrity of penile nerves and connective tissue. Sexual adverse events have been reported in clinical trials at rates of 2.1–38 % [22, 23]. The most common complaint is ED, followed by ejaculatory dysfunction and decreased libido [22]. A recent study explored the effect of long-term use of finasteride on sexual function. Erectile function declined in 11 % of patients after 1 year of therapy compared to 8 % in the placebo group. After 4 years of therapy, 18 % of patients experienced decrease in erectile function compared with 13 % in the placebo group [24]. It appears that these effects occur early in the initiation of therapy and then decreases over time.

In one study, two groups of blinded, randomized patients received 5 mg of finasteride with and without counseling regarding the potential for sexual side effects. The incidence of ED (30.9 % vs. 7.6 %), decreased libido (23.6 % vs. 7.7 %), and ejaculatory problems (16.3 % vs. 5.7 %) were significantly increased in patients who received counseling about sexual side effects of the medication versus those who did not [25, 26]. The authors conclude that a "nocebo" effect, an adverse effect that is not a direct result of the specific pharmacological action of the drug, should be taken into account when managing patients with reported sexual side effects. This latter study elucidates a common problem encountered by any physician attempting to counsel their patients regarding the potential side effects caused by the drugs mentioned in this chapter. This psychological priming can be a particularly difficult challenge in the management of sexual dysfunction in the setting of drug use.

In May 2015 the US National Institutes of Health sent out a global public health advisory recognizing a cluster of symptoms that are associated with finasteride use, called post-finasteride syndrome (PFS) [27]. PFS is a cluster of sexual, physical, and psychological/neurologic symptoms associated with 5-alpha reductase inhibitor (5ARI) use with purported persistent symptoms despite cessation of drug usage. The main sexual side effects reported were decrease in libido, erectile dysfunction, and decrease in morning erections [27]. This new syndrome (PFS) has been the basis for several studies and review articles of variable quality including a meta-analysis of 34 studies highlighting the fact that more information is needed to assess safety concerns

with finasteride, specifically for those on the lower dose of finasteride for male pattern baldness (MPB) [28]. There has been an increase of reports of nonreversible adverse events (AE) to the FDA from use of these drugs, specifically, finasteride 1 mg and finasteride 5 mg; the lower dose is used for MPB, while the higher dose has been used for LUTS/BPH. Dutasteride was never reported to cause a PFS-like symptom. Whether or not PFS is real or imagined is not answerable with current databases. More research is needed in this area due to the possible impact on patient's quality of life due to PFS.

HIV Therapy

HIV and the polypharmacy standard in the care of HIV patients have been associated with sexual dysfunction. A recent cross-sectional study of HIV patients in England estimated the prevalence of moderate to severe ED to be 33 % and moderate to severe impairment of sexual desire to be 24 % [29]. While multivariate analysis found sexual dysfunction to be common in both patients receiving anti-retroviral therapy and those naïve to the drugs, ED was found to be associated with long duration of HIV therapy [29]. A survey among a different group of HIV patients from ten different European countries demonstrated decreased libido and potency in men receiving drug regimens containing protease inhibitors as compared to protease inhibitor-naïve patients, specifically identifying protease inhibitors as a drug leading to sexual dysfunction among HIV patients [30]. Studies have shown that antiretroviral therapy is associated with increased aromatization of testosterone leading to increased serum levels of estradiol in men. It is hypothesized that the sexual dysfunction reported by patients taking antiretrovirals is secondary to these hormonal imbalances [31]. Various hormonal replacement strategies have recently been under investigation. While testosterone has been well studied in treatment of HIV-related wasting syndromes [32], several more recent reports specifically address sexual function. Letrozole [33], an aromatase inhibitor, and both parenteral and topical forms of testosterone [34] have both been shown to not only increase serum levels of testosterone but also to improve patient-reported sexual function.

Lipid-Lowering Medication

Fibrates (clofibrate, gemfibrozil, and, less frequently, bezafibrate and fenofibrate) are lipid-lowering medications that have long been associated with medication-induced sexual dysfunction [1, 4]. A case-control study of 339 age-matched men revealed that there were more impotent men in the group of patients treated with lipid-lowering medications (12 % vs. 5.6 %); and multivariate analysis showed that fibrates and statins were independent risk factors for erectile dysfunction [35]. While there are multiple trials that do not show an increased rate of sexual dysfunction in patients taking lipid-lowering medications versus placebo, there are reports of several studies in which initiation of clofibrate, gemfibrozil, and multiple statins was associated with ED. While it remains unclear what the true rates of sexual adverse events are with hypolipidemics, the mechanism which this occurs is thought to be through decreased synthesis of sex steroid hormones derived from cholesterol, namely, testosterone [36]. Some recent studies have even demonstrated some beneficial effects of statins when it comes to erectile function. One recent study reported 3.27 point increase in IIEF-5 scores in patients on statins when compared to placebo [37]. This improvement is thought to be in part to increase in nitric oxide and nitrates in the circulation, leading to endothelial relaxation and dilation. Another benefit of statin use is thought to be due to its role in suppressing RhoA/Rho kinase signaling, which therefore leads to improvement in erectile function [38].

Miscellaneous

Case reports of sexual side effects from metoclopramide, baclofen, amicar (epsilon-aminocaproic acid), disulfiram, and carbonic anhydrase inhibitors have been associated with ED [1, 4, 7].

Cytotoxic drugs that have also been implicated in drug-related ED include methotrexate [39] and thalidomide [40]. Digoxin is yet another drug that has been suggested to induce ED. The mechanism is thought to be via blockade of the Na^+,K^+-ATPase pump, resulting in a net increase in intracellular calcium and increased corporal smooth muscle tone. Others have also suggested that the chemical structure of digoxin is similar to sex steroids leading to antiandrogen activity [4].

Immunomodulators

Decreased libido and ED are commonly reported side effects experienced by male patients during antiviral therapy for chronic hepatitis C. This effect was studied in 34 male patients being treated with interferon and ribavirin [41]. Free and total testosterone decreased significantly during antiviral therapy while depression scores increased during therapy. Certain agents used in renal transplantation have been implicated in erectile function as well. The immunosuppressive agents targeting rapamycin inhibitors (i.e., sirolimus and everolimus) have been shown to result in decreases in serum testosterone levels, increases in levels of luteinizing hormone, and a disruption of spermatogenesis [42]. The impairment of gonadal function is reported to elicit ED in patients receiving these drugs.

Toxins and Recreational Drugs

In theory any process that alters the fibroelastic components of the corpora or of the associated vasculature may cause a loss of compliance and an inability to compress the tunical veins. While this may result from aging, increased cross-leaking of collagen fibers induced by nonenzymatic glycosylation, hypoxia, or altered synthesis of collagen associated with hypercholesterolemia, certain toxins have been implicated in the destruction of these fibroelastic structures and have been associated with erectile dysfunction. Arsenic exposure, for example, has been linked to ED via damage of peripheral vasculature [43]. Extensive work has also been done examining the relationship between cigarette smoking and ED [44, 45]. Chronic smoking has been identified as a major risk factor in the development of ED [44] and has been shown to have deleterious effects on vascular functioning through impairment of endothelium-dependent smooth muscle relaxation specifically by affecting NO production [44]. Animal models have demonstrated that long-term cigarette smoking is associated with impaired penile arterial flow, increased reactive oxygen species and decreased nitric oxide bioavailability, and ultrastructural damage to the vascular endothelium, to peripheral nerves, and to the corporal tissue. The precise toxins found in cigarettes mediating these changes have not been fully elucidated. However, a recent randomized, double-blind, placebo-controlled study evaluating the isolated effects of nicotine on sexual function has demonstrated that men, without significant prior exposure to nicotine, when administered nicotine gum 40 min prior to an erotic film, showed significantly reduced erectile responses as compared to age-matched controls chewing placebo gum [46], suggesting that it may be the nicotine within cigarettes that plays a role in smoke-related ED.

Both acute and chronic ethanol abuse have been implicated as a potential cause of ED [6]. The incidence of sexual dysfunction within the chronic alcoholic population has been reported to range from 8 to 54 % [4]. In addition, decreased sexual arousal, increased ejaculatory latency, and decreased orgasmic pleasure have all been noted to parallel the blood alcohol content of men. The hypothesized mechanism of these acute effects are thought to be secondary to central sedative action [4]. In mouse models, chronic ethanol exposure has been linked to impairment of endothelial function in the corpus cavernosum through reduction of NO release [47]. Chronic ethanol abuse has also been postulated to promote nerve damage via hormonal effects mediated through direct testicular damage and impairment of the hepatic estrogen metabolism. Ethanol abuse is also notorious for producing nerve damage leading to global polyneuropathy [4]. As with any disorder that affects the sacral spinal cord or the autonomic fibers to the penis, nerve damage seen in alcoholism can preclude nervous system relaxation of penile smooth muscle, thus leading to ED.

ED has been associated with opioid use, including high-dose methadone regimens for men being treated for opioid dependence. Hypoactive sexual desire, ED, and difficulty achieving orgasm as a result of opioid-induced hypogonadism and testicular failure have been reported [48–50]. Sexual dysfunction in this group of patients has been reported to be as high as 16–83.6 % [51]. While the degree of sexual dysfunction appears to be less, at 24 % [48, 51], buprenorphine, a newer drug used in the treatment of opioid dependence, has also been shown to suppress levels of testosterone, luteinizing hormone, and estradiol [49, 50]. Buprenorphine can therefore be considered as an alternative to those patients on methadone with complaints of sexual dysfunction. How androgen replacement improves sexual function in this group remains to be elucidated.

Recent evidence implicates the use of marijuana as a potential cause of ED in habitual cannabis users [52]. This study out of Italy looked at 64 men complaining of ED for at least 3 months. Patients were subjected to detailed questioning regarding recreational drug use and subsequent dynamic penile duplex sonography. Using a peak systolic velocity cutoff of 35 cm/s as a marker for organic vasculogenic dysfunction, cannabis smoking was significantly more prevalent in the organic group (78 % compared to 3 % in the non-organic ED group, $P < 0.001$) when no other vascular risk factors were present. While this study did not demonstrate a direct relationship between cannabis use and ED, based on these findings, the authors propose that cannabis use may promote early endothelial damage leading to subsequent difficulties with erections. Other recent studies have suggested that the effect of cannabinoid use on erectile function may be dose dependent, with lower doses helping with erections and higher doses inhibiting erectile function [53]. With the widespread use of cannabinoids and recent discussion of this class of drugs being used for medical purposes, more studies will be needed in order to further determine its effect on male sexual function.

Medication-Induced Ejaculatory Dysfunction

Ejaculation is the act of the sexual response cycle that is usually accompanied by an orgasm. It consists of emission and expulsion and is a reflex that coordinates sympathetic, somatic, and parasympathetic nervous systems [54]. Emission consists of secretion of the seminal vesicles, prostate, and ampulla of the vas content into the urethra creating semen [54]. Expulsion is the semen leaving the urethra via forceful contractions of the pelvic/perineal muscles [55].

Seritonergic and dopaminergic pathways also help moderate ejaculation. Anterograde ejaculation depends on the coordinated contraction of the bulbospongiosus muscle as well as the urethral smooth muscle. Any derangement in these events may lead to ejaculatory dysfunction. Medications have not only been linked to erectile dysfunction but ejaculatory dysfunction as well.

Psychotropic Medications

Antidepressants are a very common cause of medication-induced ejaculatory dysfunction, the most common being SSRIs. Delayed ejaculation has been shown to be present in about 25 % of men taking this class of medication [56]. In fact, SSRIs are used as a first-line treatment for premature ejaculation. This is thought to be due to activation of 5HT2C receptors by the SSRIs, which leads to a delay in the ejaculatory reflex arc [2]. While ED and EjD caused by antidepressant medications may be treated with PDE-5 inhibitors, studies have shown that higher doses may be needed for improvement of delayed ejaculation [56].

Antipsychotic medications have also been linked to problems with ejaculation. Studies have shown ejaculatory dysfunction to be as high as 36.1 % in patients who take antipsychotic medication [9]. Certain antipsychotics, in particular the typical antipsychotics, can exhibit α1-adrenergic antagonism and thus decrease in

vasodilation, which leads to the unwanted effects of retrograde ejaculation and priapism [57]. Atypical antipsychotics at high doses have been implicated in retrograde ejaculation and priapism as well [58]. Newer antipsychotics, such as olanzapine and aripiprazole, have lower incidences of sexual dysfunction and may be considered an alternative for treatment in patients with troublesome side effects [21].

BPH/LUTS Medications

BPH/LUTS is associated with increased risk of sexual dysfunction, including EjD. Interestingly, it has been shown that this sexual dysfunction does not worsen over time in patients who are not taking any medications for urinary symptoms [5]. Drugs used to treat LUTS due to BPH, such as α-blockers and 5ARIs, have been linked with ejaculatory dysfunction as well. Some α-blockers, such as tamsulosin and silodosin, have been associated with an increased risk (7.7 % vs. 1.1 % for placebo) [59]. Doxazosin use has been shown to be associated with lower risks of EjD, with the risk being equal to that of placebo. The mechanism behind ejaculatory function in this class of medications is thought to be due to an absence of ejaculation rather than retrograde as has been commonly assumed [60] .

5ARIs, such as dutasteride and finasteride, are also associated with higher risks of EjD than placebo [59]. A meta-analysis showed an EjD prevalence of 2.2 % of patients taking dutasteride compared to 0.8 % in the placebo group [22]. Finasteride has been associated with an increased prevalence of ejaculatory dysfunction. After 1 year of treatment, 9 % of patients experienced worsening EjD, compared with 6 % in placebo. After 4 years of treatment, this number increased to 18 %, with 12 % in the placebo group. Patients who were treated with a combination therapy of finasteride and doxazosin had a 16 and 18 % proportional decrease in ejaculatory function after 1 and 4 years of treatment, respectively [24]. Ejaculation disturbances such as anejaculation and decreased ejaculate volume have been experienced with this class of medications [22]. The mechanism behind ejaculatory dysfunction with 5ARIs is not well known; however, prostatic acinar apoptosis has been suggested.

Management of Drug-Induced Sexual Dysfunction

Although many medications can cause ED and EjD, patients frequently have concomitant risk factors that confound the clinical picture. Because the etiology of sexual dysfunction may be multifactorial, successful treatment requires management of underlying risk factors and concomitant medical conditions. The majority of the patients with sexual dysfunction also have coexisting obesity, coronary artery disease (CAD), hypertension, or diabetes. It is important to note that lifestyle changes may greatly improve sexual function in people with these comorbidities [60]. And in fact, as reviewed above, many of these patients also present with LUTS secondary to bladder outlet obstruction from benign prostatic hyperplasia (BPH). Patients being treated for mental illness and experiencing sexual dysfunction can also be some of the most difficult patients to manage. Differentiating organic from psychogenic causes is highly challenging as depression is one of the most common causes of psychogenic sexual dysfunction and almost all patients in this population present with some overlap of psychogenic and organic factors. In any patient presenting with sexual dysfunction, psychogenic causes should also be given high consideration. Psychogenic causes are thought to mediate sexual dysfunction by inhibiting reflexogenic responses at the spinal cord level, thereby blocking activation of vasodilator outflow to the penis. Excess sympathetic stimulation as is typical with generalized anxiety or performance anxiety can also increase penile smooth muscle tone.

If there is a strong association between the institution of a drug and the onset of sexual dysfunction, alternative medications should be considered. Otherwise, it is often practical to treat ED or EjD without attempting multiple changes of medication choice, as it may be difficult to establish a causal role for the drug. Depending on

the drug, the nature of the problem being treated by the drug, and the known pathophysiology of sexual dysfunction, various approaches have been previously suggested. What is becoming clear is that the treatment of this challenging problem often necessitates multidisciplinary planning and potential involvement of a urologist, especially when changes in medication therapy alone do not eliminate sexual dysfunction. While the utility of hormone replacement for drug-induced hypogonadism continues to be studied, various forms of androgen replacement exist and should be considered in the appropriate patient.

PDE-5 inhibitors have been shown to attenuate drug-induced sexual side effects in multiple arenas, including EjD. PDE-5 inhibitors are even safe to use in patients on antihypertensive medications when appropriate measures are taken [10]. Addition of sildenafil or tadalafil has also been very successful in patients with antidepressant-induced sexual dysfunction as well as BPH/LUTS-induced sexual dysfunction [13, 61, 62]. Recognition and management of medication-induced sexual dysfunction have also been shown to significantly increase medication adherence, therefore decreasing comorbidities of the disease being treated [60].

When oral medications do not provide relief, the urologist has an armamentarium of alternative therapies and strategies to improve sexual function and satisfaction. Highly motivated patients should be counseled about alprostadil suppositories, vacuum erection devices, and intracavernosal injection therapy when appropriate. Surgery with implantable penile devices should be considered a last resort and be reserved for patients with irreversible damage to their penile vasculature and microanatomy or who experience sexual dysfunction refractory to medical treatment. Finally, as more drugs are recognized as potential risk factors for ED or EjD, doctors should not ignore consideration of other organic and nonorganic causes in their differential. As mentioned previously, appropriately managing sexual dysfunction, regardless of the cause, can greatly improve medical compliance as well as the patient's quality of life.

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References

1. McVary K. Sexual dysfunction. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 17th ed. New York: McGraw-Hill Companies Inc; 2008. p. 296–300.
2. Xin ZC, Zhu YC, Yuan YM, et al. Current therapeutic strategies for premature ejaculation and future perspectives. Asian J Androl. 2011;13:550–7.
3. Slag MF, Morley JE, Elson MK, et al. Impotence in medical clinic outpatients. JAMA. 1983;249:1736–40.
4. Wein AJ, Van Arsdalen KN. Drug-induced male sexual dysfunction. Urol Clin North Am. 1988;15:23–31.
5. Fwu CW, Kirkali Z, McVary KT, Burrows PK, Eggers PW, Kusek JW. Cross-sectional and longitudinal associations of sexual function with lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol. 2015;193:231–8.
6. Francis ME, Kusek JW, Nyberg LM, Eggers PW. The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males. J Urol. 2007;178:591–6. discussion 6.
7. Stadler T, Bader M, Uckert S, Staehler M, Becker A, Stief CG. Adverse effects of drug therapies on male and female sexual function. World J Urol. 2006;24:623–9.
8. Manolis A, Doumas M. Antihypertensive treatment and sexual dysfunction. Curr Hypertens Rep. 2012;14:285–92.
9. Fusco F, Franco M, Longo N, Palmieri A, Mirone V. The impact of non-urologic drugs on sexual function in men. Arch Ital Urol Androl. 2014;86:50–5.
10. Doumas M, Douma S. The effect of antihypertensive drugs on erectile function: a proposed management algorithm. J Clin Hypertens (Greenwich). 2006;8:359–64.
11. Karavitakis M, Komninos C, Theodorakis PN, et al. Evaluation of sexual function in hypertensive men receiving treatment: a review of current guidelines recommendation. J Sex Med. 2011;8:2405–14.
12. Gacci M, Corona G, Salvi M, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol. 2012;61:994–1003.
13. Gur S, Sikka SC, Chandra S, et al. Alfuzosin attenuates erectile dysfunction in rats with partial bladder outlet obstruction. BJU Int. 2008;102:1651–7.

14. Gregorian RS, Golden KA, Bahce A, Goodman C, Kwong WJ, Khan ZM. Antidepressant-induced sexual dysfunction. Ann Pharmacother. 2002;36:1577–89.
15. Rosen RC, Marin H. Prevalence of antidepressant-associated erectile dysfunction. J Clin Psychiatry. 2003;64 Suppl 10:5–10.
16. Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. Drug Saf. 2014;37:19–31.
17. Finkel MS, Laghrissi-Thode F, Pollock BG, Rong J. Paroxetine is a novel nitric oxide synthase inhibitor. Psychopharmacol Bull. 1996;32:653–8.
18. Fava M, Nurnberg HG, Seidman SN, et al. Efficacy and safety of sildenafil in men with serotonergic antidepressant-associated erectile dysfunction: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2006;67:240–6.
19. Nurnberg HG, Gelenberg A, Hargreave TB, Harrison WM, Siegel RL, Smith MD. Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Am J Psychiatry. 2001;158:1926–8.
20. Nurnberg HG, Hensley PL, Gelenberg AJ, Fava M, Lauriello J, Paine S. Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. JAMA. 2003;289:56–64.
21. Baggaley M. Sexual dysfunction in schizophrenia: focus on recent evidence. Hum Psychopharmacol. 2008;23:201–9.
22. Erdemir F, Harbin A, Hellstrom WJ. 5-Alpha reductase inhibitors and erectile dysfunction: the connection. J Sex Med. 2008;5:2917–24.
23. Wessells H, Roy J, Bannow J, et al. Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. Urology. 2003;61:579–84.
24. Fwu CW, Eggers PW, Kirkali Z, McVary KT, Burrows PK, Kusek JW. Change in sexual function in men with lower urinary tract symptoms/benign prostatic hyperplasia associated with long-term treatment with doxazosin, finasteride and combined therapy. J Urol. 2014;191:1828–34.
25. Mondaini N, Gontero P, Giubilei G, et al. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? J Sex Med. 2007;4:1708–12.
26. Welliver C, Butcher M, Potini Y, McVary KT. Impact of alpha blockers, 5-alpha reductase inhibitors and combination therapy on sexual function. Curr Urol Rep. 2014;15:441.
27. Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. Am J Mens Health. 2015;9:222–8.
28. Belknap SM, Aslam I, Kiguradze T, et al. Adverse event reporting in clinical trials of finasteride for androgenic alopecia: a meta-analysis. JAMA Dermatol. 2015;151:600–6.
29. Asboe D, Catalan J, Mandalia S, et al. Sexual dysfunction in HIV-positive men is multi-factorial: a study of prevalence and associated factors. AIDS Care. 2007;19:955–65.
30. Schrooten W, Colebunders R, Youle M, et al. Sexual dysfunction associated with protease inhibitor containing highly active antiretroviral treatment. AIDS. 2001;15:1019–23.
31. Lamba H, Goldmeier D, Mackie NE, Scullard G. Antiretroviral therapy is associated with sexual dysfunction and with increased serum oestradiol levels in men. Int J STD AIDS. 2004;15:234–7.
32. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA. 2000;283:763–70.
33. Richardson D, Goldmeier D, Frize G, et al. Letrozole versus testosterone: a single-center pilot study of HIV-infected men who have sex with men on highly active anti-retroviral therapy (HAART) with hypoactive sexual desire disorder and raised estradiol levels. J Sexual Med. 2007;4:502–8.
34. Scott JD, Wolfe PR, Anderson P, Cohan GR, Scarsella A. Prospective study of topical testosterone gel (AndroGel) versus intramuscular testosterone in testosterone-deficient HIV-infected men. HIV Clin Trials. 2007;8:412–20.
35. Bruckert E, Giral P, Heshmati HM, Turpin G. Men treated with hypolipidaemic drugs complain more frequently of erectile dysfunction. J Clin Pharm Ther. 1996;21:89–94.
36. Rizvi K, Hampson JP, Harvey JN. Do lipid-lowering drugs cause erectile dysfunction? A systematic review. Fam Pract. 2002;19:95–8.
37. Cai X, Tian Y, Wu T, Cao CX, Bu SY, Wang KJ. The role of statins in erectile dysfunction: a systematic review and meta-analysis. Asian J Androl. 2014;16:461–6.
38. La Vignera S, Condorelli RA, Vicari E, Calogero AE. Statins and erectile dysfunction: a critical summary of current evidence. J Androl. 2012;33:552–8.
39. Penninga EI, Larsen HK, Andersen SE. Impotence caused by methotrexate treatment. Ugeskrift Laeger. 2008;170:354.
40. Murphy PT, O'Donnell JR. Thalidomide induced impotence in male hematology patients: a common but ignored complication? Haematologica. 2007;92:1440.
41. Kraus MR, Schafer A, Bentink T, et al. Sexual dysfunction in males with chronic hepatitis C and antiviral therapy: interferon-induced functional androgen deficiency or depression? J Endocrinol. 2005;185:345–52.
42. Huyghe E, Zairi A, Nohra J, Kamar N, Plante P, Rostaing L. Gonadal impact of target of rapamycin inhibitors (sirolimus and everolimus) in male patients: an overview. Transpl Int. 2007;20:305–11.

43. Freeman K. Arsenic and erectile dysfunction: drinking contaminated well water increases risk. Environ Health Perspect. 2008;116:A172.
44. Tostes RC, Carneiro FS, Lee AJ, et al. Cigarette smoking and erectile dysfunction: focus on NO bioavailability and ROS generation. J Sex Med. 2008;5:1284–95.
45. McVary KT, Carrier S, Wessells H. Smoking and erectile dysfunction: evidence based analysis. J Urol. 2001;166:1624–32.
46. Harte CB, Meston CM. Acute effects of nicotine on physiological and subjective sexual arousal in nonsmoking men: a randomized, double-blind, placebo-controlled trial. J Sex Med. 2008;5:110–21.
47. Aydinoglu F, Yilmaz SN, Coskun B, Daglioglu N, Ogulener N. Effects of ethanol treatment on the neurogenic and endothelium-dependent relaxation of corpus cavernosum smooth muscle in the mouse. Pharmacol Rep. 2008;60:725–34.
48. Bliesener N, Albrecht S, Schwager A, Weckbecker K, Lichtermann D, Klingmuller D. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. J Clin Endocrinol Metab. 2005;90:203–6.
49. Hallinan R, Byrne A, Agho K, McMahon C, Tynan P, Attia J. Erectile dysfunction in men receiving methadone and buprenorphine maintenance treatment. J Sex Med. 2008;5:684–92.
50. Hallinan R, Byrne A, Agho K, McMahon CG, Tynan P, Attia J. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. Int J Androl. 2009;32(2):131–9.
51. Yee A, Loh HS, Hisham Hashim HM, Ng CG. The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study. J Sex Med. 2014;11:22–32.
52. Aversa A, Rossi F, Francomano D, et al. Early endothelial dysfunction as a marker of vasculogenic erectile dysfunction in young habitual cannabis users. Int J Impot Res. 2008;20:566–73.
53. Shamloul R, Bella AJ. Impact of cannabis use on male sexual health. J Sex Med. 2011;8:971–5.
54. Lowe FC. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: sexual function. BJU Int. 2005;95 Suppl 4:12–8.
55. Giuliano F, Clement P. Pharmacology for the treatment of premature ejaculation. Pharmacol Rev. 2012;64:621–44.
56. Seidman S. Ejaculatory dysfunction and depression: pharmacological and psychobiological interactions. Int J Impot Res. 2006;18 Suppl 1:S33–8.
57. Compton MT, Miller AH. Priapism associated with conventional and atypical antipsychotic medications: a review. J Clin Psychiatry. 2001;62:362–6.
58. Loh C, Leckband SG, Meyer JM, Turner E. Risperidone-induced retrograde ejaculation: case report and review of the literature. Int Clin Psychopharmacol. 2004;19:111–2.
59. Gacci M, Ficarra V, Sebastianelli A, et al. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. J Sex Med. 2014;11:1554–66.
60. Scranton RE, Goldstein I, Stecher VJ. Erectile dysfunction diagnosis and treatment as a means to improve medication adherence and optimize comorbidity management. J Sex Med. 2013;10:551–61.
61. Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev. 2013;5: CD003382.
62. Gur S, Kadowitz PJ, Hellstrom WJ. Guide to drug therapy for lower urinary tract symptoms in patients with benign prostatic obstruction: implications for sexual dysfunction. Drugs. 2008;68:209–29.

Oral Prescription Therapy for Erectile Dysfunction

12

Nelson E. Bennett Jr.

Introduction

Currently, oral pharmacotherapy is the initial form of therapy for men who do not have a contraindication for its use. Most commonly the agents of choice are from the phosphodiesterase type 5 inhibitor (PDE5i) family. Prior to the widespread popularity of these drugs in the late 1990s, the choices for the noninvasive treatment of ED consisted of yohimbine and trazodone. Other substances, such as testis sicca, testosterone, ginseng, caffeine, barbituric acid, saw palmetto, and cayenne fruit among others, have been prescribed with dubious results. While the most effective agents act peripherally, medications with a central nervous system mechanism of action have proven more difficult to develop.

This chapter on oral prescription therapy for erectile dysfunction will review those agents with central and peripheral nervous system action. This chapter also touches briefly on those medications which may be available in some countries, although not officially be approved for ED treatment.

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Centrally Acting Agents

Yohimbine

Yohimbine is an indole alkaloid that has been isolated from the bark of the *Pausinystalia* yohimbe tree. This tree is indigenous to Central Africa. It is also found in the *Rauwolfia* root and the dried bark of *Aspidosperma quebracho*. Extracts from the yohimbe tree containing yohimbine have been used in traditional medicine in West Africa as an aphrodisiac for hundreds of years. Prior to the launch of sildenafil in the USA, it was the widely use for treatment of erectile dysfunction. Currently, it has been relegated to use in over-the-counter male enhancement supplements.

Mechanism of Action

Yohimbine is a competitive antagonist selective for alpha-2 adrenoceptors, which are located on nerve terminals and receptors and to mediate inhibition of transmitter release. The presynaptic release of norepinephrine is increased by an alpha-2 antagonist resulting in increased sympathetic outflow. Yohimbine may also interact with alpha-1 adrenoceptors and, in high concentrations, serotonin, vasoactive intestinal peptidergic (VIPergic), and dopamine receptors. Yohimbine has monoamine oxidase inhibitory effects. In the cavernosa, yohimbine binds to the alpha-2 adrenoceptors preventing the contractility

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of the corporal tissue that would normally be induced by catecholamines. Centrally, yohimbine exhibits central activity by interacting with the serotonergic systems resulting in a profound effect in sexual behavior.

Pharmacology and Dosing

Yohimbine's oral absorption appears to be poor, although there appears to be highly variable bioavailability. This may be the result of extensive first-pass metabolism [1]. According to one pharmacokinetic study, a 10 mg oral dose of yohimbine produced a peak plasma concentration within 45 min, and the half-life for plasma clearance was 0.2–1.1 h. Yohimbine is lipophilic and it crosses the blood-brain barrier [1]. Yohimbine has an elimination half-life of less than 1 h, while an active metabolite, 11-hydroxy-yohimbine, has a half-life of about 6 h [1]. In a study of 32 patients, 24 displayed one-compartment elimination, while eight displayed two-compartment elimination [2]. Less than 1 % of the oral dose was recovered unchanged in the urine within 24 h [2].

The most common dosing regimen for this medication is 5–15 mg three times daily [3, 4]. Men are informed that 6–8 weeks of treatment is required for maximal effect.

Side Effects

Yohimbine may exacerbate hypertension or cause arrhythmias and tremors [5, 6]. It also interacts with tricyclic antidepressants, so that pressor effects occur at lower doses, and may potentiate the alpha-adrenergic blocking properties of phenothiazines [7]. Adverse reactions include mania, bronchospasm, a systemic lupus-like syndrome, and agranulocytosis [7].

Efficacy

The success of the medication ranges from 0 to 72 % [8–11]. A meta-analysis of seven large yohimbine studies revealed that may be slightly more efficacious than placebo [12]. The popularization of phosphodiesterase inhibitors combined with the side effect profile of yohimbine has consigned the medication to the nutritional supplement arena.

Conclusion

Despite being widely available, yohimbine has limited use in the medical treatment of sexual issues.

Apomorphine

Apomorphine was first synthesized by Matthiessen in 1869. Apomorphine does not actually contain morphine or its skeleton nor does it bind to opioid receptors. Other than its use in erectile dysfunction, it has been used in the treatment of alcoholism, Parkinson's disease, and Alzheimer's. In alcoholism, it is now hypothesized that it can reboot the dopaminergic system and renew the "reward pathway." Because of the strong dopaminergic action of apomorphine, it has a profound effect on Parkinson's disease [13]. In fact, when administered subcutaneously, apomorphine is the most effective dopamine agonist. Apomorphine is a potential therapeutic option for Alzheimer's disease. Apomorphine has been reported to be both an inhibitor of the amyloid beta protein (Aβ) fiber formation and a promoter of Aβ degradation [13].

Apomorphine stimulates the dopamine receptors in the hypothalamus enhancing the effect of natural dopamine that is produced as a result of sexual stimulation, thereby assisting in the generation of an erection [14–16]. In 1995 Heaton et al. reported positive results for orally administered apomorphine in seven out of ten patients with psychogenic impotence [17].

Mechanism of Action

Apomorphine is a potent, nonselective dopaminergic receptor agonist previously used in the treatment of ED [17]. It has a balanced affinity for D1 and D2 receptors. The reported binding affinity (Ki) for D1-like receptors is 101 nM; for D5, 10 nM; for D2-like receptors, 32 nM; for D3, 26 nM; and for D4, 2.6 nM [18]. Many of these receptors are located in the paraventricular nucleus and medial preoptic area. Erections induced by apomorphine rely on the parasympathetic oxytocinergic nerve fibers to begin the erection cascade. As an aporphine alkaloid,

apomorphine lacks the narcotic properties and other opiate effects of its parent compound (morphine), although it does possess strong emetogenic properties.

Pharmacology and Dosing

Apomorphine has a very rapid onset of action combined with a brief duration of effect [19]. The duration of apomorphine action, after a single administration, is dose and mode of administration dependent, with an elimination half-life ranging from 30 to 90 min [20]. Drug absorption, volume of distribution, plasma clearance, and half-lives are similar for all modes of administration. Many routes of apomorphine administration have been used in clinical practice, but sublingual and nasal are preferred. Oral administration is not efficient because of apomorphine's significant first-pass hepatic metabolism and poor bioavailability. Apomorphine is lipophilic and freely crosses the blood-brain barrier. Apomorphine is a high clearance drug (3–5 L/kg/h) that is mainly excreted and metabolized by the liver, and the remainder is excreted unchanged in the urine [20].

Although not approved for use in many countries (including the USA), it is still available for purchase. Apomorphine is available in 2 and 3 mg doses. The medication may be taken sublingually once every 8 h and no more than three times in 24 h. Apomorphine should be taken approximately 20 min prior to sexual activity.

Side Effects

Reported side effects of using apomorphine sublingual or subcutaneously are nausea 30 %, headache 2.9 %, dizziness 20 %, yawning 40 %, somnolence 35 %, sweating 1.2 %, vasodilation 0.9 %, vomiting 30 %, and hypotension 20 % [21].

Efficacy

Apomorphine has been shown significantly greater action than placebo. Randomized, prospective trials have not shown that apomorphine is superior or equal to sildenafil. In fact, these studies show that 94–95 % of men preferred sildenafil for superior efficacy and decrease adverse side effects [22, 23].

Conclusion

Apomorphine has been taken off of the US market secondary to poor efficacy and a significant incidence of undesirable adverse effects. The mediation remains available through quasi-legal outlets.

Trazodone

Trazodone hydrochloride is an oral antidepressant with anxiolytic and sedative/hypnotic effects. It is sometimes used to treat ED because of its reported increase in libido and sexual function.

Mechanism of Action

There are several mechanisms of action exhibited by trazodone. It is a selective inhibition of serotonin reuptake, as well as an antagonist of α2-adrenergic receptors [24, 25]. Antagonizing these receptors results in penile vascular and corporal smooth muscle relaxation, thereby enhancing arterial inflow and generating an erection.

Pharmacology and Dosing

Trazodone is well absorbed after oral administration, with mean peak blood levels obtained at about one hour after ingestion. Half-life is 3–9 h and is highly protein bound. The drug is extensively metabolized with 70–75 % excreted in the urine within 3 days. For adults with depression, trazodone may be initiated at 75 mg BID with the possibility of escalating the dose to maximum dose of 600 mg/day [26]. There is no generally accepted dose of trazodone for treating ED [26].

Side Effects

Side effects of trazodone are similar to those of serotonin reuptake inhibitors; headache, nausea, vomiting, changes in bowel habits, change in appetite, dizziness, and priapism are most common.

Efficacy

In a study of patients with psychologically based ED, Kurt et al. found that those men who ingested 150 mg/day were significantly more likely to

have three or more successful attempts at sexual intercourse than placebo [27]. Montorsi et al. reported on 50 % of men that used that trazodone 50 mg/day combined with yohimbine 5 mg three times daily were significantly more likely to have erections sufficient for penetration [28].

Conclusion

The primary use of trazodone is the treatment of major depression; however, off-label use for the treatment of erectile dysfunction is common. This drug may be an alternative adjunctive treatment in some anxious or depressed men. Trazodone may be useful in the treatment of selective serotonin reuptake inhibitor-induced sexual dysfunction alone or in combination with PDE5i [29, 30].

Peripherally Acting Agents

Papaverine was the first phosphodiesterase inhibitor (PDEi) utilized for treating ED. Papaverine is a nonselective PDEi that is derived from the opium poppy. This alkaloid is also used in the treatment of visceral spasm and vasospasm. It is a nonselective PDEi that promotes cavernosal smooth muscle relaxation by inhibiting both PDE5 and PDE3, thereby increasing intracellular levels of cGMP and cAMP.

The first oral phosphodiesterase-5 inhibitor (PDE5i) that was approved in the USA for the treatment of ED was sildenafil citrate. Not only did the introduction of sildenafil revolutionize the treatment of ED, it altered the way the global community thinks about sexual disorders and helped foster open discussion regarding treatment.

Erectile Physiology

The generation of a penile erection is a complex vascular phenomenon that results in smooth muscle relaxation, arterial dilation, and venous occlusion [31]. Without the multifaceted interplay between adrenergic, cholinergic, and nonadrenergic/non-cholinergic (NANC) systems, as well as sexual stimulation, the corpus cavernosum smooth muscle tone contracts resulting in penile flaccidity [32–34].

As illustrated in Fig. 12.1, upon sexual stimulation, the parasympathetic nervous system and NANC nerve terminals activate, facilitating the release of nitric oxide (NO) from the sinusoidal endothelium. NO activates guanylyl cyclase, which converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP) [35]. Cyclic GMP is a catalyst that leads to the phosphorylation of and activation of potassium and calcium channels. The paucity of intracellular calcium facilitates cavernosal smooth muscle relaxation and dilation of helicine arterioles. As the cavernosa fill with blood, the sinusoidal spaces exert increased compressive pressure on the subtunical venous plexus and emissary veins preventing the exodus of blood from the penis and preserving the erection [36].

Phosphodiesterase type 5 (PDE5) enzymatically hydrolyzes the conversion of cGMP to guanosine monophosphate (GMP) facilitating detumescence after orgasm or cessation of sexual stimulation. Penile flaccidity is helped by the outpouring of adrenergic compounds released during the sympathetic control of ejaculation. This leads to vasoconstriction and cessation of NO release from the sinusoidal endothelium resulting in smooth muscle contraction and loss of erection. Other signaling molecules like vasoactive intestinal polypeptide (VIP) and calcitonin gene-related peptide (CGRP) play a role in erectile physiology [37].

Phosphodiesterase type 5 inhibitor (PDE5i) medications prevent the conversion of cGMP to GMP, thereby maintaining or prolonging the erectile state.

Phosphodiesterase Type 5 Inhibitors (PDE5i)

Since the introduction of sildenafil, many PDE5i medications have been developed and marketed. Although each PDE5i has different pharmacokinetics, pharmacodynamics, and side effects, they all have a similar mechanism of action; PDE5i drugs selectively inhibit PDE5 facilitating elevated levels of cGMP.

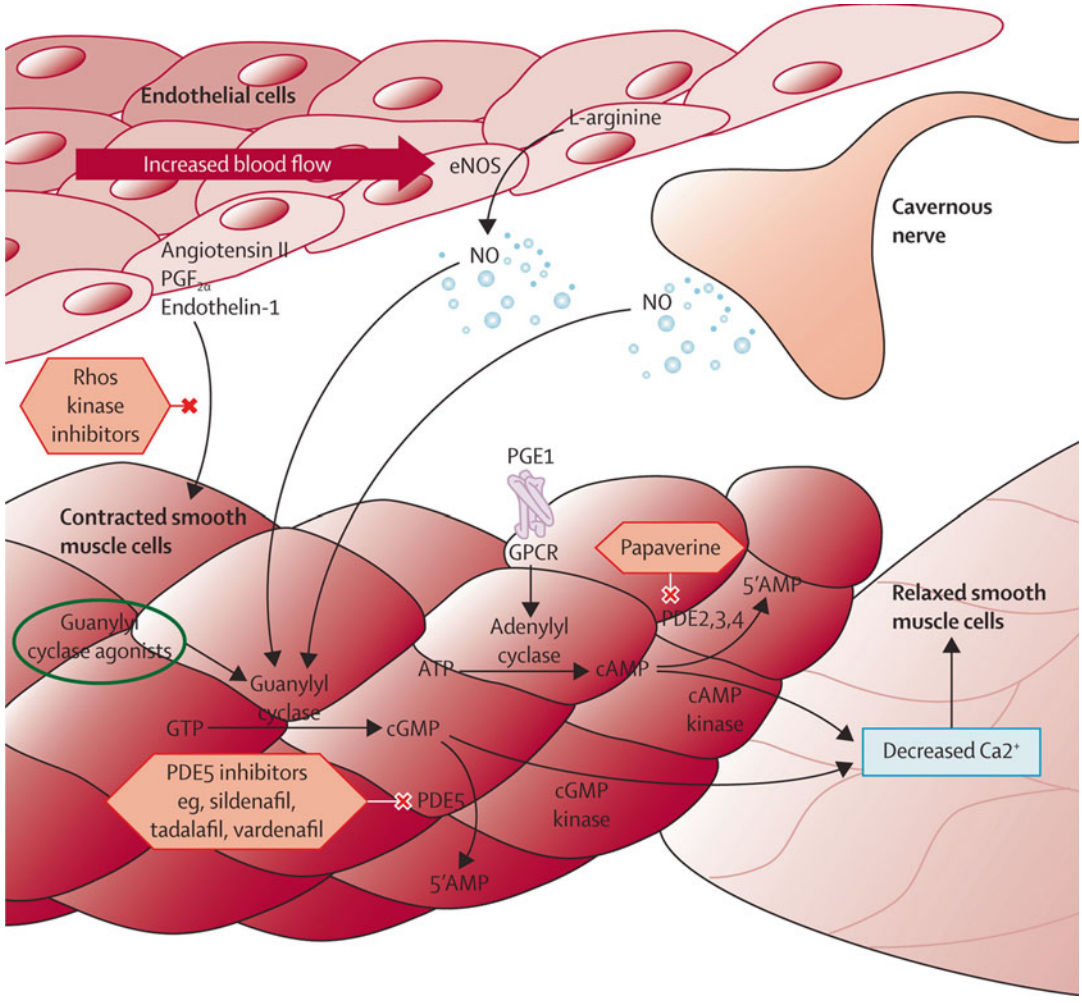

Fig. 12.1 Physiology of penile smooth muscle relaxation (Used with permission from Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381: 153–65)

Sildenafil

As previously mentioned, sildenafil was synthesized by pharmaceutical chemists working in an English research facility in England [38]. The medication was initially studied for use in hypertension and angina pectoris, but clinical trials revealed that the drug had poor effect on angina, but generated substantial erectile capacity in the study participants [39].

Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41 % (range 25–63 %) [40]. Both sildenafil and its metabolite have terminal half-lives of about 4 h. Maximum observed plasma concentrations are reached within 30–120 min (median 60 min) of oral dosing in the fasted state [41]. When taken with a high-fat meal, the rate of absorption is reduced, and T_{max} is delayed 60 min and a 29 % reduction in serum concentration [42]. Sildenafil is cleared predominantly by the CYP3A4 (major route) hepatic microsomal isoenzyme [40]. The major circulating metabolite results from *N*-desmethylation of sildenafil and has an in vitro potency for PDE5 approximately 50 % of the parent drug [40]. Sildenafil is excreted as metabolites predominantly in the feces and to a lesser extent in the urine [40].

Vardenafil

The FDA approved vardenafil in August of 2003. Vardenafil was initially a co-marketing arrangement between three pharmaceutical companies—Bayer, GlaxoSmithKline, and Schering-Plough—as a response to the success of sildenafil. Their marketing strategy highlighted the superior gastrointestinal absorption of vardenafil as compared to sildenafil.

In vitro studies have shown that vardenafil is a selective inhibitor of PDE5. The inhibitory effect of vardenafil is more selective on PDE5 than for other known phosphodiesterases [43]. Vardenafil is rapidly absorbed with absolute bioavailability of approximately 15 % [44]. Maximum observed plasma concentrations after a 20 mg dose are reached 30–120 min (median 60 min) after oral dosing in the fasted state. Food-effect studies were conducted which showed that high-fat meals caused a reduction in C_{max} by 18 % [45, 46]. Vardenafil is eliminated predominantly by hepatic metabolism mainly by CYP3A4 and to a minor extent, CYP2C isoforms. Its metabolite shows a phosphodiesterase selectivity profile similar to that of vardenafil and an in vitro inhibitory potency for PDE5 28 % of that of vardenafil [44]. The terminal half-life of vardenafil and its primary metabolite is approximately 4–5 h. After oral administration, vardenafil is excreted as metabolites predominantly in the feces.

Tadalafil

Tadalafil began life as IC351, a cardiovascular drug. It began initial cardiovascular testing in 1993 [47]. Once sildenafil began to show promise as an ED agent (1994), the company that developed tadalafil applied for a patent. Phase I trials began in 1995. In November of 2003, the FDA approved tadalafil for sale in the USA [47].

Tadalafil may be given over a dose range of 2.5–20 mg. Once per day dosing of 2.5 mg or 5 mg is possible [43]. Steady-state plasma concentrations are attained within 5 days of once per day dosing, and exposure is approximately 1.6-fold greater than after a single dose. After single dose, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 min and 6 h (median time of 2 h). The rate and absorption of tadalafil are not influenced by food [43].

Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The mean terminal half-life is 17.5 h in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61 %) and in the urine (approximately 36 %) [43].

Avanafil

Avanafil was approved by the FDA on April 27, 2012 [48]. The advantage of avanafil is that it has very fast onset of action compared with other PDE5 inhibitors. Avanafil is rapidly absorbed after oral administration, with an average time to maximal plasma concentration (T_{max}) of 30–45 min in the fasted state. If avanafil is taken with a high-fat meal, the rate of absorption is reduced, with decreased serum levels between 24 and 39 %. Avanafil is cleared predominantly by hepatic metabolism by the CYP3A4. After oral administration, avanafil is excreted as metabolites predominantly in the feces and to a lesser extent in the urine. Avanafil has a terminal elimination half-life of approximately 5 h.

Side Effects

The side effects and contraindications are listed in Table 12.1 [46].

Efficacy

There are currently four different PDE5i medications on the market in the USA. Which criteria should providers use to select the appropriate agent for a particular patient? There have been no head-to-head trials comparing the available PDE5is. In fact, Lue and Carson reported that there was no practicable way to directly compare sildenafil, vardenafil, and tadalafil with the available data at that time [49]. Nevertheless, investigators have compiled data in the form of meta-analyses [50, 51]. In Table 12.2, the absolute treatment effect is has been compiled from several studies for the PDE5 inhibitors available in the USA. The absolute treatment effect suggests that tadalafil and vardenafil are more effective PDE5 inhibitors in terms of Global Assessment Questionnaire-question 1 (GAQ-1), International Index of Erectile Function-Erectile Function Domain (IIEF-EFD), Sexual Encounter Profile question 2 (SEP-2), and Sexual Encounter

Table 12.1 Side effects and contraindication of PDE5i agents

Agent	Dose	Adverse effects	Contraindications
Sildenafil	25–100 mg	Headache, flushing, dyspepsia, rhinitis, altered vision, palpitations	Nitrates, certain retrovirals, agents metabolized through CYP3A hepatic system, retinitis pigmentosa, fluctuating dose of alpha blockers
Vardenafil	5–20 mg	Headache, flushing, rhinitis, dyspepsia, palpitations	Nitrates, certain retrovirals, agents metabolized through CYP3A hepatic system, retinitis pigmentosa, fluctuating dose of alpha blockers, prolongation of QT interval, concomitant use of class I antiarrhythmic
Tadalafil	2.5–20 mg	Headache, rhinitis, dyspepsia, myalgia	Nitrates, certain retrovirals, agents metabolized through CYP3A hepatic system, retinitis pigmentosa, fluctuating dose of alpha blockers
Avanafil	100–200 mg	Headache, rhinitis, dyspepsia	Nitrates, certain retrovirals, agents metabolized through CYP3A hepatic system, retinitis pigmentosa, fluctuating dose of alpha blockers

Table 12.2 Absolute treatment effect for FDA-approved PDE5 inhibitors

	GAQ-1	IIEF-EFD	SEP-2	SEP-3
PDE5i	Absolute effect, mean (95 % CI)	Absolute effect, mean (95 % CI)	Absolute effect, mean (95 % CI)	Absolute effect, mean (95 % CI)
Sildenafil	0.73	7.68	10.48	29.10
Tadalafil	0.75	9.21	29.70	48.07
Vardenafil	0.73	8.39	29.22	48.13
Avanafil	0.46	N/A	N/A	N/A
Placebo	0.24	1.64	1.86	11.92

Profile question 3 (SEP-3) [51–54]. All in all, what is important to focus on is that all four PDE5 inhibitors have similar success rates with small differences in safety and efficacy endpoints. In addition to increased penile rigidity, phosphodiesterase inhibitors have also shown that they can effect improvements in orgasmic function, patient and partner sexual satisfaction, improved quality of life, and improvement in depressive symptoms [55, 56].

Atypical Drugs

Arginine

L-arginine is a semi-essential or conditionally essential amino acid that is abundant in dairy, meat, seafood, grains, and legumes. L-arginine is precursor in the production of nitric oxide, which is the essential vasodilatory compound that facilitates erectogenic action [57]. A prospective randomized, double-blind placebo-controlled study of men taking 5 g of L-arginine per day concluded that a third of the men in the trial experienced enhanced sexual function, but only in men with abnormal nitric oxide metabolism [58]. Other studies have found that men using L-arginine had significant improvements in sexual function without side effects.

Ginseng

Korean red ginseng is thought to stimulate erectile function either through promotion of the nitric oxide system or its saponin content [59, 60]. In a 2002 double-blind, placebo-controlled,

crossover study, Hong reported that mean International Index of Erectile Function scores were significantly higher in patients treated with Korean red ginseng (900 mg, 3 times daily) than in those who received placebo [60].

Horny Goat Weed

Horny goat weed is a naturally occurring plant of the *Epimedium* species that may enhance erectile function, as well as produce aphrodisiac effects. The active component is icariin which has PDE5 inhibitor-like activities [61, 62]. Icariin also has been linked to contributing to an increase in the circulating levels of testosterone [63]. In many Western countries, the horny goat weed has been marketed as "Natural Viagra."

Ginkgo Biloba

Ginkgo has been purported to increase circulation and is thought to improve memory, global cognitive function, and erectile dysfunction. Ginkgo extracts may improve sexual function by enhancing blood flow to the brain, as well as the penis. Unfortunately, the positive cognitive benefits of this supplement have not been realized, and the benefits to sexual functioning have been questioned [64–67]. Three randomized placebo-controlled trials have not found significant increases in sexual function with ginkgo extracts [68–70].

Practical Considerations in Administration and Use of Phosphodiesterase Inhibitors

In addition to lifestyle modifications, the administration of PDE5 inhibitors is part of the first-line treatment strategy for men with erectile dysfunction. Over the past several years, varied and incorrect medication administration instructions have been communicated to patients leading to suboptimal erectile response and frustration.

Optimal Intake Strategy

Despite the pharmacodynamic/pharmacokinetic data listed in the package inserts for sildenafil and vardenafil, these agents boast "real world" duration of action from one to 12 h. Peak serum levels occur at about 1 h after administration. Complicating matters, the gastrointestinal absorption of sildenafil and vardenafil is negatively affected by the ingestion of lipid-laden foods. A fatty meal may delay and diminish absorption 20–50 %. Routinely, I ask the patient to take vardenafil or sildenafil 2 h before a meal to maximize the effect of the medication. If he ingests the medication at 5 o'clock, he should expect to be ready for sexual relations from 7 o'clock to midnight.

Tadalafil has a longer onset of action compared to vardenafil and sildenafil. Optimal results occur when the medication is taken at least 4 h prior to sexual activity. The effects will last for 24 h or longer. Food does not interfere with the gastrointestinal absorption of tadalafil; however, excessive alcohol intake will delay gastric emptying leading to belated commencement of activity. Currently, the best way of avoiding the temporal restrictions of vardenafil, sildenafil, and single-dose tadalafil (10–20 mg) is to use daily tadalafil (2.5–5 mg). With this iteration of tadalafil, serum levels are therapeutic after 3 days, greatly enhancing spontaneity of intimacy.

I recommend that the patient start therapy by using the maximal dose of sildenafil, vardenafil, or tadalafil. The patient may decrease the dose if they have an excellent response or experience side effects. It is uncommon for a PDE5 inhibitor that will provide sustainable results after only one tablet. We will council patients to take these medications over at least four separate occasions before making a final decision of the efficacy of any individual PDE5i.

Lastly, we impress upon patients that if a properly taken PDE5 inhibitor is not successful in generating an erection, it is very unlikely that switching to a different oral agent will have a significantly different result. The most compelling reason to switch to a different PDE5i is to avoid bothersome side effects or to better accommodate

a certain lifestyle. Trying multiple PDE5 inhibitors typically leads to frustration and financial strife on the part of the patient. It would be prudent for the man to explore more advanced and invasive erectile dysfunction treatments when met with PDE5i failure.

Cardiovascular Considerations

Patients with history of myocardial infarction who do not have ischemia on stress test and are asymptomatic are at low risk for a repeat myocardial infarction (MI). The American Heart Association's Guidelines do not disallow intimate sexual activity as early as 1 week after MI in the stable patient [71]. Resumption of sexual activity 1 week after uncomplicated MI is reasonable in the asymptomatic man with moderate physical activity (3–5 METS) [72]. This recommendation is born out of data that men engaged in cardiac rehabilitation programs 1 week post-MI has proven safe and effective. Additionally, PDE5is are not contraindicated in this cohort of men as long as the patient is not in possession of nitrate-containing medications.

Nitrates

As previously stated, PDE5 inhibitors inhibit the degradation of cGMP. However, nitroglycerin and isosorbide dinitrate (as well as other nitrates) increase intracellular production of cGMP. The simultaneous use of these agents results in accretion cGMP, which will result in a drastic drop in systolic and diastolic blood pressure. As such, the concomitant use of nitrates and PDE5 inhibitors is contraindicated.

In emergent situations in which cardiac-based chest pain occurs in a man who has recently consumed a PDE5 inhibitor, a beta-blocker or calcium channel blocker can be used as substitutes [73]. In the instance of avanafil, a total of 12 h should pass before nitrate-containing medication can be administered [43]. For sildenafil and vardenafil, 24 h should elapse [43]. Forty-eight hours should pass between tadalafil and nitrate administration [43].

Men in possession of nitrate-containing medications deserve special mention. Under no circumstances should these men receive a prescription for a PDE5 inhibitor. If the nitroglycerin-containing medication prescriber is willing to formally grant permission (in writing) for the patient to discard the nitrate, I will then allow the patient to obtain a PDE5i script. In these cases, I have found that over 50 % of men are allowed to stop the nitroglycerine medication.

References

1. Sturgill MG, Grasing KW, Rosen RC, et al. Yohimbine elimination in normal volunteers is characterized by both one- and two-compartment behavior. J Cardiovasc Pharmacol. 1997;29:697–703.
2. Piletz JE, Segraves KB, Feng YZ, Maguire E, Dunger B, Halaris A. Plasma MHPG response to yohimbine treatment in women with hypoactive sexual desire. J Sex Marital Ther. 1998;24:43–54.
3. Guay AT, Spark RF, Jacobson J, Murray FT, Geisser ME. Yohimbine treatment of organic erectile dysfunction in a dose-escalation trial. Int J Impot Res. 2002;14:25–31.
4. Pushkar D, Segal AS, Bagaev AG, Nosovitskii PB. Yohimbine in the treatment of erectile dysfunction. Urologiia. 2002;6:34–7.
5. Grossman E, Rosenthal T, Peleg E, Holmes C, Goldstein DS. Oral yohimbine increases blood pressure and sympathetic nervous outflow in hypertensive patients. J Cardiovasc Pharmacol. 1993;22:22–6.
6. Onrot J, Goldberg MR, Biaggioni I, Wiley RG, Hollister AS, Robertson D. Oral yohimbine in human autonomic failure. Neurology. 1987;37:215–20.
7. De Smet PA, Smeets OS. Potential risks of health food products containing yohimbe extracts. BMJ. 1994;309:958.
8. Kunelius P, Hakkinen J, Lukkarinen O. Is high-dose yohimbine hydrochloride effective in the treatment of mixed-type impotence? A prospective, randomized, controlled double-blind crossover study. Urology. 1997;49:441–4.
9. Teloken C, Rhoden EL, Sogari P, Dambros M, Souto CA. Therapeutic effects of high dose yohimbine hydrochloride on organic erectile dysfunction. J Urol. 1998;159:122–4.
10. Vogt HJ, Brandl P, Kockott G, et al. Double-blind, placebo-controlled safety and efficacy trial with yohimbine hydrochloride in the treatment of nonorganic erectile dysfunction. Int J Impot Res. 1997;9:155–61.
11. Pittler MH, Ernst E. Trials have shown yohimbine is effective for erectile dysfunction. BMJ. 1998;317:478.
12. Ernst E, Pittler MH. Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials. J Urol. 1998;159:433–6.

13. Himeno E, Ohyagi Y, Ma L, et al. Apomorphine treatment in Alzheimer mice promoting amyloid-beta degradation. Ann Neurol. 2011;69:248–56.
14. Lal S, Tesfaye Y, Thavundayil JX, et al. Apomorphine: clinical studies on erectile impotence and yawning. Prog Neuropsychopharmacol Biol Psychiatry. 1989; 13:329–39.
15. Lal S, Ackman D, Thavundayil JX, Kiely ME, Etienne P. Effect of apomorphine, a dopamine receptor agonist, on penile tumescence in normal subjects. Prog Neuropsychopharmacol Biol Psychiatry. 1984;8: 695–9.
16. Lal S, Laryea E, Thavundayil JX, et al. Apomorphine-induced penile tumescence in impotent patients--preliminary findings. Prog Neuropsychopharmacol Biol Psychiatry. 1987;11:235–42.
17. Heaton JP, Morales A, Adams MA, Johnston B, El-Rashidy R. Recovery of erectile function by the oral administration of apomorphine. Urology. 1995; 45:200–6.
18. Hsieh GC, Hollingsworth PR, Martino B, et al. Central mechanisms regulating penile erection in conscious rats: the dopaminergic systems related to the proerectile effect of apomorphine. J Pharmacol Exp Ther. 2004;308:330–8.
19. Gancher ST, Woodward WR, Boucher B, Nutt JG. Peripheral pharmacokinetics of apomorphine in humans. Ann Neurol. 1989;26:232–8.
20. Gancher ST, Bennett W, English J. Studies of renal function in animals chronically treated with apomorphine. Res Commun Chem Pathol Pharmacol. 1989; 66:163–6.
21. Pfeiffer RF, Gutmann L, Hull Jr KL, Bottini PB, Sherry JH, Investigators APOS. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. Parkinsonism Relat Disord. 2007;13:93–100.
22. Gontero P, D'Antonio R, Pretti G, et al. Clinical efficacy of Apomorphine SL in erectile dysfunction of diabetic men. Int J Impot Res. 2005;17:80–5.
23. Pavone C, Curto F, Anello G, Serretta V, Almasio PL, Pavone-Macaluso M. Prospective, randomized, crossover comparison of sublingual apomorphine (3 mg) with oral sildenafil (50 mg) for male erectile dysfunction. J Urol. 2004;172:2347–9.
24. Eardley I. New oral therapies for the treatment of erectile dysfunction. Br J Urol. 1998;81:122–7.
25. Krege S, Goepel M, Sperling H, Michel MC. Affinity of trazodone for human penile alpha1-andalpha2-adrenoceptors. BJU Int. 2000;85:959–61.
26. Fink HA, MacDonald R, Rutks IR, Wilt TJ. Trazodone for erectile dysfunction: a systematic review and meta-analysis. BJU Int. 2003;92:441–6.
27. Kurt U, Ozkardes H, Altug U, Germiyanoglu C, Gurdal M, Erol D. The efficacy of anti-serotoninergic agents in the treatment of erectile dysfunction. J Urol. 1994;152:407–9.
28. Montorsi F, Strambi LF, Guazzoni G, et al. Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. Urology. 1994;44:732–6.
29. Stryjer R, Spivak B, Strous RD, et al. Trazodone for the treatment of sexual dysfunction induced by serotonin reuptake inhibitors: a preliminary open-label study. Clin Neuropharmacol. 2009;32:82–4.
30. Taneja R. A rational combination pharmacotherapy in men with erectile dysfunction who initially failed to oral sildenafil citrate alone: a pilot study. J Sex Med. 2007;4:1136–41.
31. Andersson KE, Wagner G. Physiology of penile erection. Physiol Rev. 1995;75:191–236.
32. Andersson KE. Pharmacology of penile erection. Pharmacol Rev. 2001;53:417–50.
33. Andersson KE. Neurophysiology/pharmacology of erection. Int J Impot Res. 2001;13 Suppl 3:S8–17.
34. Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381:153–65.
35. Clement P, Giuliano F. Anatomy and physiology of genital organs—men. Handb Clin Neurol. 2015;130:19–37.
36. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am. 2005;32:379–95. v.
37. Burnett AL. Role of nitric oxide in the physiology of erection. Biol Reprod. 1995;52:485–9.
38. Boolell M, Allen MJ, Ballard SA, et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. Int J Impot Res. 1996;8:47–52.
39. Sung BJ, Hwang KY, Jeon YH, et al. Structure of the catalytic domain of human phosphodiesterase 5 with bound drug molecules. Nature. 2003;425:98–102.
40. Wallis RM. The pharmacology of sildenafil, a novel and selective inhibitor of phosphodiesterase (PDE) type 5. Nihon Yakurigaku Zasshi. 1999;114 Suppl 1:22P–6.
41. Corbin JD, Francis SH. Pharmacology of phosphodiesterase-5 inhibitors. Int J Clin Pract. 2002;56: 453–9.
42. Carrier S. Pharmacology of phosphodiesterase 5 inhibitors. Can J Urol. 2003;10 Suppl 1:12–6.
43. Staff P, editor. (2015). Physicians' desk reference. 69th ed. PDR Network; 2015.
44. Bischoff E. Vardenafil preclinical trial data: potency, pharmacodynamics, pharmacokinetics, and adverse events. Int J Impot Res. 2004;16 Suppl 1:S34–7.
45. Rajagopalan P, Mazzu A, Xia C, Dawkins R, Sundaresan P. Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. J Clin Pharmacol. 2003;43:260–7.
46. Setter SM, Iltz JL, Fincham JE, Campbell RK, Baker DE. Phosphodiesterase 5 inhibitors for erectile dysfunction. Ann Pharmacother. 2005;39:1286–95.
47. Coward RM, Carson CC. Tadalafil in the treatment of erectile dysfunction. Ther Clin Risk Manag. 2008;4: 1315–30.

48. Kyle JA, Brown DA, Hill JK. Avanafil for erectile dysfunction. Ann Pharmacother. 2013;47:1312–20.
49. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int. 2005;96:257–80.
50. Wang H, Yuan J, Hu X, Tao K, Liu J, Hu D. The effectiveness and safety of avanafil for erectile dysfunction: a systematic review and meta-analysis. Curr Med Res Opin. 2014;30:1565–71.
51. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol. 2013; 63:902–12.
52. Hellstrom WJ, Gittelman M, Karlin G, et al. Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl. 2002;23:763–71.
53. Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol. 2002;168:1332–6.
54. Porst H, Rosen R, Padma-Nathan H, et al. 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;13:192–9.
55. Hatzichristou D, Cuzin B, Martin-Morales A, et al. Vardenafil improves satisfaction rates, depressive symptomatology, and self-confidence in a broad population of men with erectile dysfunction. J Sex Med. 2005;2:109–16.
56. Montorsi F, Althof SE. Partner responses to sildenafil citrate (viagra) treatment of erectile dysfunction. Urology. 2004;63:762–7.
57. Andrew PJ, Mayer B. Enzymatic function of nitric oxide synthases. Cardiovasc Res. 1999;43:521–31.
58. Chen J, Wollman Y, Chernichovsky T, Iaina A, Sofer M, Matzkin H. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. BJU Int. 1999;83:269–73.
59. Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. Int J Impot Res. 1995;7:181–6.
60. 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: 2070–3.
61. Jiang Z, Hu B, Wang J, et al. Effect of icariin on cyclic GMP levels and on the mRNA expression of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in penile cavernosum. J Huazhong Univ Sci Technolog Med Sci. 2006;26:460–2.
62. Dell'Agli M, Galli GV, Dal Cero E, et al. Potent inhibition of human phosphodiesterase-5 by icariin derivatives. J Nat Prod. 2008;71:1513–7.
63. Zhang ZB, Yang QT. The testosterone mimetic properties of icariin. Asian J Androl. 2006;8:601–5.
64. Laws KR, Sweetnam H, Kondel TK. Is Ginkgo biloba a cognitive enhancer in healthy individuals? A meta-analysis. Hum Psychopharmacol. 2012;27:527–33.
65. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009:CD003120.
66. Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. J Sex Marital Ther. 1998;24:139–43.
67. Corazza O, Martinotti G, Santacroce R, et al. Sexual enhancement products for sale online: raising awareness of the psychoactive effects of yohimbine, maca, horny goat weed, and Ginkgo biloba. Biomed Res Int. 2014;2014:841798.
68. Sikora RSM, Engelke B, et al. Randomized placebo-controlled study on the effects of oral treatment with gingko biloba extract in patients with erec-tile dysfunction. J Urol. 1998;159: 240A (Abstract #917).
69. Kang BJ, Lee SJ, Kim MD, Cho MJ. A placebo-controlled, double-blind trial of Ginkgo biloba for antidepressant-induced sexual dysfunction. Hum Psychopharmacol. 2002;17:279–84.
70. Wheatley D. Triple-blind, placebo-controlled trial of Ginkgo biloba in sexual dysfunction due to antidepressant drugs. Hum Psychopharmacol. 2004;19: 545–8.
71. Kushner FG, Hand M, Smith Jr SC, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-Elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. Circulation. 2009;120:2271–306.
72. Clark AM, Catto S, Bowman G, Macintyre PD. Design matters in secondary prevention: individualization and supervised exercise improves the effectiveness of cardiac rehabilitation. Eur J Cardiovasc Prev Rehabil. 2011;18:761–9.
73. Rosen RC, Jackson G, Kostis JB. Erectile dysfunction and cardiac disease: recommendations of the second princeton conference. Curr Urol Rep. 2006;7:490–6.

Vacuum Therapy for Erectile Dysfunction

13

Sarah L. Hecht and Jason C. Hedges

Introduction

Among the myriad treatment options available for erectile dysfunction, arguably none is as safe and cost-effective as vacuum therapy. A nonpharmacologic, noninvasive erectile aid, vacuum therapy uses negative pressure to distend the corporal sinusoids and increase blood flow to the penis. A basic vacuum erection device (VED) comprises two components, a cylinder which surrounds the penis and a pump which evacuates air from within the cylinder creating a vacuum. Following penile engorgement, a constricting band may be deployed onto the base of the penis to occlude venous outflow and maintain the erection. This band transforms the VED into a vacuum constriction device (VCD). VEDs and VCDs have been available commercially since the 1980s. They fell out of favor with the advent of phosphodiesterase 5 (PDE5) inhibitors, but given the cost and side effects of alternative therapies, these devices have been regaining popularity in recent years [1, 2].

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History

John King, an American physician, is credited with developing the first vacuum erection device. His so-called glass exhauster was a negative pressure mechanical device capable of producing a temporary artificial erection [3]. Once the device was removed, the erection disappeared. It was not until 1917 that film actor Otto Lederer patented "a ring of elastic material placed on the root of the penis," a constriction band to be used in conjunction with vacuum therapy to maintain an erection [4]. Other patents followed; however, credit for popularizing the modern VCD goes to Geddings D. Osbon, Sr. His "youth equivalent device" was reportedly perfected through 20 years of personal use [5, 6].

In 1982 the device received FDA approval and became commercially available as the Osbon ErecAid [7]. Vacuum therapy gained widespread acceptance in the urologic community in 1990, when Lue wrote an editorial in the *Journal of Urology* stating that he recommended vacuum constriction devices as first-line therapy to nearly all of his patients with erectile dysfunction [8]. Further validation came in 1996 when VCDs were listed as one of three treatment alternatives recommended by the American Urological Association Clinical Guidelines Panel on the treatment of organic erectile dysfunction [9].

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Mechanism and Design

The vacuum constriction device has three components: a plastic cylinder into which the penis is placed, a pump which removes air from the cylinder, and an elastic constriction band (Fig. 13.1). The open base of the cylinder is pressed securely against the pubis. Lubricant is often helpful to attain an airtight seal. In most modern devices, the pump is integrated to allow for single-handed operation. When activated, this removes air from the cylinder creating a vacuum which leads to distension of the corporal sinusoids and subsequent penile engorgement. Of note, all FDA-approved cylinders have pop-off valves, which limit the amount of pressure held within the chamber. Following engorgement, a penile constriction ring can be deployed onto the base of the penis, which restricts venous outflow to maintain the erect state. A release valve relieves the negative pressure, and the cylinder is removed (Fig. 13.2). The constriction band must be removed within 30 min to avoid ischemia. In addition to mechanical effects on blood flow, there is some thought that VEDs stimulate nitrous oxide release, which mediates corporal smooth muscle relaxation [10].

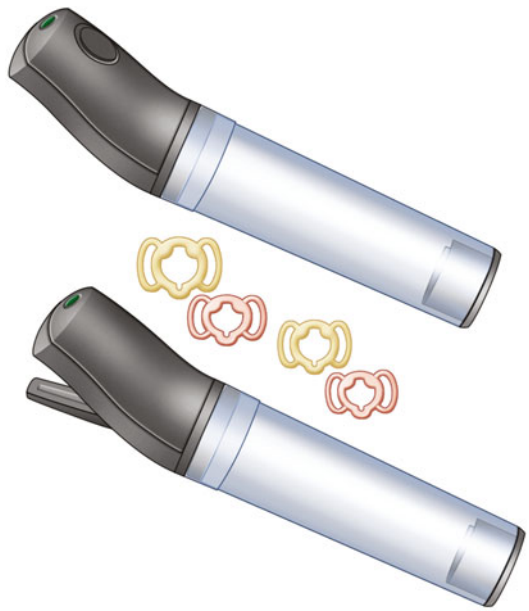

Fig. 13.1 Model of a vacuum constriction device. Both battery-operated (*top*) and manual (*bottom*) pump mechanisms are depicted. Elastic constriction rings of varying sizes are available

Clinical Evidence

Because vacuum devices are both nonpharmacologic and noninvasive, they have not been subjected to the strict clinical trials required of PDE5 inhibitors, intracavernosal injections, and penile prostheses. Most of the data regarding vacuum therapy come in the form of single-center observational studies. The clinical efficacy of vacuum constriction devices is summarized in Table 13.1.

Early studies by Drs. Perry Nadig and John Witherington in the 1980s were instrumental in demonstrating the safety and efficacy of vacuum therapy. Nadig tested a vacuum constriction device in 35 men with organic impotence. Thirty two of those men achieved rigidity sufficient for penetration, and at follow-up 8–22 months later, 24 of 35 (69 %) were still using the device with high satisfaction [11]. Nadig was also the first to provide objective data on penile rigidity. Longitudinal buckling pressures of 454 g, the minimum criterion used in sleep laboratory evaluations, were achieved in 27 of 35 (77 %) patients. Several years later, Witherington surveyed over 1500 users of VCDs and found that 92 % patients achieved erections satisfactory for intercourse with no serious side effects or complications [12]. Nearly eighty percent of users reported having intercourse at least every 2 weeks. A subsequent study of 100 men using the VCD followed, which reported a 68 % satisfaction rate [13].

Cookson and Nadig were the first to look at long-term results with VCDs [14]. Patients completed a questionnaire after 3 and 29 months of use. Approximately 70 % of subjects used the device regularly. Both patients and partners reported satisfaction rates above 80 % at short-term and long-term follow-up. Satisfaction with the quality of the erections (hardness, penile length, and circumference) was rated greater than 90 %. Long-term users enjoyed more frequent intercourse, which was sustained beyond the first year. Long-term success has since been

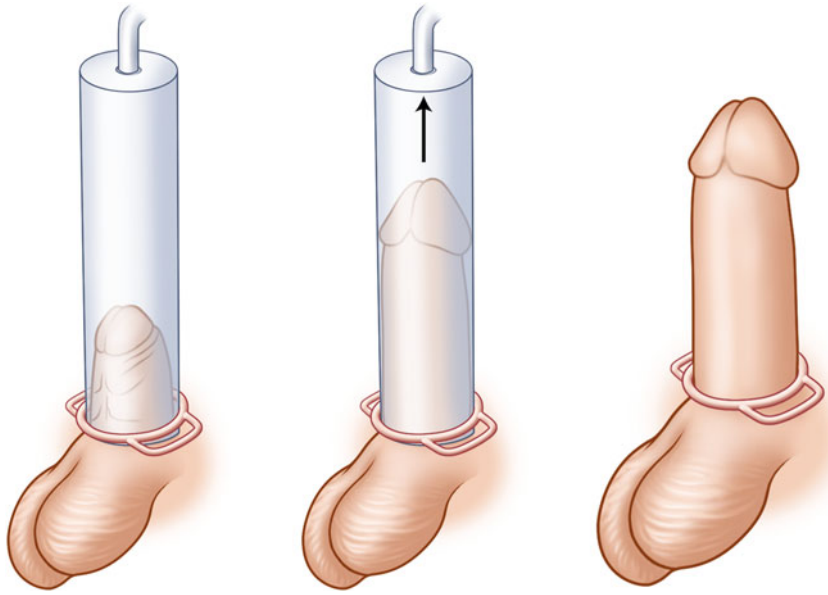

Fig. 13.2 Achieving erection with a vacuum constriction device. The first panel shows initial placement of the VCD over the flaccid penis, taking care not to involve the scrotum. The second panel shows engorgement of the penis as air is pumped out of the cylinder, creating a vacuum. The final panel shows an erect penis with the constriction band in place

Table 13.1 Efficacy of vacuum constriction devices in erectile dysfunction

First author	Year	*N*	Mean follow-up	Results
Nadig [11]	1986	35	8–22 months	91 % satisfactory erections, 80 % use regularly
Witherington [12]	1989	1517	8.6 months	92 % satisfactory erections, 77 % use regularly. Best results with partial impotence
Sidi [13]	1990	100	7.9 months	68 % satisfaction rate
Turner [16]	1991	45	12 months	87 % satisfactory erections. Attrition rate 20 %
Cookson [14]	1993	216	29 months	70 % use regularly. >80 % patient and partner satisfaction
Segenreich [15]	1993	150	25 months	75 % satisfactory erections. Of those, 64 % purchased VED. Long-term use rate of 43 % overall, but >90 % in those who purchased VED
Blackhard [93]	1993	45	NA	64 % purchased VED. Long-term use 44 % overall, 69 % of those who purchased VED
Meinhardt [21]	1993	74	NA	31 % satisfaction rate. All patients had previous failed alternate therapies
Vrijhof [19]	1994	67	NA	50 % satisfactory erections, best results with nonneurogenic ED
Baltaci [94]	1995	49	12.8 months	Attrition rate 33 %. Of the remaining 67 %, >80 % satisfaction rate. Best results with arteriogenic ED
Kolettis [95]	1995	50	7.6 months	76 % satisfactory erections. 56 % satisfaction rate. Satisfaction unrelated to severity of ED
Derouet [81]	1999	110	28 months	Attrition rate was 58 %. Of long-term users (primarily those who did not respond to ICI), 98 % satisfaction and 85 % partner satisfaction
Dutta [20]	1999	129	37 months	Attrition rate was 65 %. Remaining 35 % were satisfied. Best results for moderate ED, not mild or severe

corroborated. Segenreich et al. reported that of 64 men who purchased a VCD after successfully testing it in a physician's office, 90 % became long-term, satisfied users [15]. A prospective study by Turner et al. redemonstrated excellent immediate and long-term results, with adequate erections in 87 % of subjects and only a 20 % attrition rate after 12 months [16].

In an attempt to quantify the efficacy of VCDs, Bosshardt et al. evaluated penile rigidity with the RigiScan nocturnal penile tumescence monitor [17]. Penile rigidity of 70 % is considered satisfactory for intercourse [18]. In the same study, penile blood gas analysis revealed that ischemia could result 30 min after applying the constriction rings. This led to the recommendation that constriction rings be removed after 30 min.

Not all series report such high success. Vrijhof et al. found that only 50 % of men attain satisfactory erections with VCDs [19]. Dutta and Eid reported a 35 % satisfaction rate based on attrition, despite significant instruction on device use [20]. Meinhardt et al. report a mere 31 % satisfaction rate in patients who have failed prior therapies, though they admit that patient selection is a clear confounder [21]. In a study by Derouet et al., 20 % of subjects rejected the VCD outright, and an additional 38 % stopped using the device over time. Reasons cited for rejecting or discontinuing vacuum therapy include inadequate erections, difficulty using the device, lack of spontaneity, partner rejection, discomfort, and loss or change of romantic partner. While attrition rates may seem high, it is important to note that they compare favorably with adherence rates of intracorporeal injection (ICI), which has early dropout rates of up to 40 % and up to 56 % within 1 year [22–24]. Those who do continue to use VCDs long term tend to be highly satisfied.

VCDs in Diabetes

The association between diabetes mellitus and erectile dysfunction dates back to medieval Persia, when physician Avicenna observed a "collapse of sexual function" in patients with sweet urine [25]. This link was again described by Scottish surgeon John Rollo, who chronicled diabetic men seized with *coitus nullus*: *erectio nunquam: ne quidem semel rigescit* ("null coitus: never erect: not even once does it stiffen.") [26]. Erectile dysfunction has since become a well-established complication of diabetes affecting over half of all diabetic men, a prevalence 2–4 times higher than is seen in the nondiabetic population [27, 28].

In a study by Price et al., 33 of 44 diabetic men using VCDs (75 %) reported erections satisfactory for intercourse with a mean usage rate of 5.5 times per month [29]. Of the remaining 11 men, eight could not achieve adequate erections and three others could, but their partners found the vacuum erection device an unacceptable erectile aid. Arauz-Pacheco also showed a 75 % success rate in 12 diabetic men with erectile dysfunction and diabetic neuropathy [30]. Bodansky et al. studied 19 diabetic patients with erectile dysfunction and EMG-proven neuropathy [31]. After 6 months, 11 (58 %) of patients continued to use the VCD with an average rate of four times monthly. Self-assessment values for sexual satisfaction, partner's sexual satisfaction, and self-esteem significantly increased. Israilov studied VCD efficacy in 162 diabetic men with ED, most of whom had failed sildenafil citrate [32]. Although 114 (70.4 %) responded well, only 19 (11.7 %) patients agreed to continue its use. Almost uniformly, patients complained of intolerable pain from even the loosest constriction bands. While PDE5 inhibitors remain the mainstay of ED treatment in diabetics, vacuum devices are a viable second line, noninvasive alternative to those patients who accept them.

VCD in Spinal Cord Injury

The vast majority of patients with spinal cord injury (SCI) suffer some element of erectile dysfunction [33, 34]. Patients with upper motor neuron lesions may achieve spontaneous erections; however, these tend to be transient [33]. Those with lower motor neuron lesions suffer more profound erectile failure. Several studies have looked at vacuum therapy within the spinal cord injury

population. Early studies of VCD therapy in spinal cord-injured patients suggested that vacuum therapy led to more frequent intercourse and increased sexual satisfaction of both patients and their partners [35, 36]. Heller et al. reported on long-term outcomes with VCD use in 17 men with chronic neurologic impotence. After a mean follow-up of 21 months, more than half of patients continued to use the device, and frequency of intercourse increased from 0.3 to 1.5 times per week [37].

Denil et al. studied 20 men with SCI using VCDs for erectile dysfunction [38]. After 3 months, 93 % of men reported rigidity sufficient for vaginal penetration, with an average duration of 18 min. Interestingly, those numbers decreased at 6 month follow-up, at which time only 41 % of men were satisfied with their VCD. Premature loss of erection was the most common complaint. Chancellor et al. measured penile rigidity following VCD use in SCI patient with a mean increase in rigidity of 57 % (range 30–80 %) [39].

In a prospective, multicenter survey, Watanabe et al. evaluated the efficacy of injection therapy and VCDs [40]. Patients using vacuum therapy reported a sexual intercourse mean of five times per month as compared with three times per month in those using injections. More recently, Moemen et al. compared PDE5 inhibitors, ICI, and VCDs in SCI patients. All therapies yielded excellent results [41]. Seventy percent of men using the VED reported normal IIEF-EF scores after treatment, compared with none before treatment. By comparison, 90 % of patients using sildenafil or injections reported normal IIEF scores after treatment, and these therapies were preferred due to convenience.

It should be noted that while vacuum therapy is widely accepted as one of the safest therapeutic options for ED, spinal cord-injured patients tend to be at higher risk for complications. In the study by Watanabe et al., two patients reported subcutaneous hemorrhage, and one reported penile ischemia. Similarly, Rivas et al. describe two cases of subcutaneous hemorrhage in spinal cord-injured VCD users on anticoagulation, as well as a single case of penile gangrene [42]. Presumably this is due to decreased sensation and subsequent excessive suction or constriction.

Combination Therapy

While monotherapy with VCDs is both safe and effective, vacuum therapy need not be used in isolation. Multiple studies show that VCDs can serve as an effective adjunct to other erectile aids. The most common multimodal therapy combines PDE5 inhibitors and VCDs [43, 44]. Chen et al. studied 161 men with ED who initially trialed monotherapy with VED or sildenafil [43]. In the 41 patients who failed monotherapy, combination therapy was used. All 41 patients reported greater satisfaction with combined treatment, as well as significant improvement across all IIEF domains. The combination of PDE5i and vacuum therapy is particularly effective in the post-prostatectomy population [45, 46].

Several studies have also demonstrated synergistic effects between vacuum therapy and intracavernosal, intraurethral, and topical agents, leading to enhanced organic erectile function and decreased need for a constriction device [47–49]. Vacuum therapy may also enhance penile prostheses [50, 51]. Soderdahl et al. reported that 11 of 12 men with penile prostheses who concomitantly used VEDs described a subjective increase in length and girth, as well as satisfaction [50]. Vacuum therapy has even been shown to enhance sex therapy for patients with psychogenic erectile dysfunction [52].

Other Indications for Vacuum Therapy

Post-prostatectomy Penile Rehabilitation

Perhaps the greatest driver of the resurgence of vacuum erectile therapy is its application in penile rehabilitation following prostatectomy. Even with surgical modifications such as nerve-sparing and a robot-assisted laparoscopy, post-prostatectomy ED rates in contemporary series

range from 30 to 87 % [53–55]. Sexual dysfunction following prostatectomy, which includes erectile dysfunction and changes in penile shape and size, has profound detrimental effects of quality of life [56, 57]. The pathophysiology of ED following prostatectomy is complex and multifactorial. Among other mechanisms postoperative cavernosal nerve neurapraxia is nearly universal, leading to a transient loss of erectile function. Without arterial inflow the corpora become hypoxic, and cavernosal smooth muscle apoptosis and collagen deposition ensue [58–60]. This in turn leads to penile shortening and damage to the veno-occlusive mechanism necessary for erectile function [60–63]. Provoking an artificial erection during this period of neurapraxia is thought to decrease hypoxia and thus cavernosal fibrosis. This has led to the development of post-prostatectomy penile rehabilitation protocols.

Currently, there is no consensus as to the optimal rehabilitative regimen. Given its cost-effectiveness, low complication rate, and independence from the nitric oxide pathway, vacuum therapy is an excellent candidate for post-prostatectomy penile rehabilitation [64]. In a recent survey of American Urological Association members, vacuum therapy is the second most commonly used modality for penile rehabilitation, and the British Society for Sexual Medicine recommends VEDs as first-line therapy along with PDE5 inhibitors [65, 66]. A recent pilot study by Welliver et al. demonstrated that vacuum therapy does indeed improve penile oxygenation, confirming a physiologic rational for VEDs in penile rehabilitation. The constriction ring causes local hypoxia and is typically not used in rehabilitation protocols, though occasional use for intercourse is permitted [17, 67].

It is only within the past decade that vacuum therapy has been studied in penile rehabilitation protocols. A summary of the data is tabularized in Table 13.2. In a 2006 randomized prospective trial, Raina et al. studied 109 men undergoing radical prostatectomy who were randomized either to daily vacuum therapy starting 1 month after surgery or to no penile rehabilitation [68]. The treatment group enjoyed a slightly higher rate of natural erections sufficient for intercourse (17 % vs. 11 %), though the rates remain disappointing. Surprisingly, there was no difference between nerve-sparing and non-nerve-sparing procedures. Moreover, those using their VED were less likely to perceive a decrease in penile length and circumference (23 % vs. 85 %).

Table 13.2 Vacuum therapy (VT) in post-prostatectomy penile rehabilitation

First author	Year	*N*	Design	Results
Baniel [72]	2001	85	Progressive regimen, VT was first line	92 % adequate erections with VT, only 14 % agreed to continue VT at home
Gontero [73]	2005	76	Progressive regimen, VT was second line	Adequate erections in 8, 52, and 60 % of pts using sildenafil, VT, and ICI, respectively
Raina [68]	2006	109	VT vs. no therapy	Higher rate of natural erections (17 % vs. 11 %) and decreased perceived penile shrinkage (23 % vs. 85 %) in VT group
Köhler [70]	2007	28	Early vs. late post-op VT	Early intervention led to higher IIEF scores (12.4 vs. 3.0 at 6 months) and decreased risk of penile shortening >2 cm (12 % vs. 45 %)
Dalkin [69]	2007	42	VT compliance vs. stretched penile length	Decreased loss of penile length >1 cm in patients compliant with VT protocol
Engel [45]	2011	26	Tadalafil vs. tadalafil + VT	At 12 months, 92 % of combination group achieve vaginal penetration vs. 57 % with tadalafil only. Increased IIEF in combination group. Better compliance with VT than tadalafil
Basal [46]	2013	203	PDE5i, VT, PDE5i + VT vs. no therapy	PDE5i + VT most effective in decreasing time to recovery of erectile function

The following year, Dalkin and Christopher conducted a prospective study of 42 men to assess the effect of VED on stretched penile length following prostatectomy [69]. Vacuum therapy lasted for 90 days starting the day after catheter removal. Patients compliant with the protocol had significantly decreased risk of loss of length greater than 1.0 cm (3 %) as compared with data from earlier studies in which 48 % of men had significant length reduction.

Kohler et al. tested stretched flaccid penile length in a prospective randomized trial comparing early vs. late penile rehabilitation with vacuum therapy [70]. Twenty-eight men were assigned to start vacuum therapy either 1 month or 6 months following radical prostatectomy. The early intervention group had significantly higher IIEF scores. In addition, early intervention dramatically decreased the incidence penile shortening. At 12 months, two of 17 (12 %) of men in the early rehabilitation group and five of 11 (45 %) in the control group lost at least 2 cm of penile length.

These studies are in their infancy and are limited by lack of standardization—the optimum timing and length of therapy are not known. More recent studies seem to indicate that combining oral PDE5 inhibitors with vacuum therapy yields the best result, particularly following robotic nerve-sparing prostatectomy [45, 46]. Despite some promising data, not all agree that vacuum therapy is an effective mode of penile rehabilitation, most notably citing high attrition rates and the lack of intention to treat analyses [71]. Attrition is indeed significant. For instance, Baniel et al. studied a progressive penile rehabilitation regimen which included vacuum therapy. While 92 % of men developed adequate erections with vacuum therapy, only 14 % continued using their VED at home [72]. Moreover, some argue that penile rehabilitation as a whole remains largely unproven with regard to long-term recovery of natural erections [71, 73]. Certainly more rigorous study would be enlightening.

Penile Lengthening

Vacuum therapy has long been rumored to enhance penile length. A recent study by Aghamir et al. debunked this myth. Thirty-seven men with stretched penile length less than 10 cm used a VED for 6 months. Mean penile length increased from 7.6 to 7.9 cm, a statistically insignificant change, though it should be noted that 30 % of patients were satisfied with the vacuum device [74].

On the other hand, there is new enthusiasm for preoperative VED therapy prior to penile prosthesis implantation. Moskovic reported a case of a single post-prostatectomy patient who used a VED for length preservation prior to penile prosthesis implantation. His stretched penile length increased 2.3 cm after vacuum therapy [75]. A subsequent single institution trial of 750 patients who underwent a 2-month preoperative VED protocol revealed encouraging results. Since instituting the vacuum therapy protocol, average cylinder length of implanted penile prostheses increased from 18.4 to 22.0 cm. Moreover, there was a significant decrease in postoperative pain which allowed for earlier device cycling, as well as improved patient satisfaction with postoperative length [76, 77]. Vacuum therapy can also be remarkably effective following penile prosthesis explantation, which leads to cavernosal fibrosis and notoriously refractory erectile dysfunction [78].

Penile Straightening

In recent years, significant interest has developed in penile traction therapy for penile straightening and lengthening in patients with Peyronie's disease. While non-vacuum traction devices are better studied, there are data to suggest vacuum therapy is a reasonable option [79]. Raheem et al. showed a modest decrease in penile curvature (5–25°) in 21 out of 31 men who used daily

vacuum traction to treat their Peyronie's disease [80]. Sixteen of these 21 patients were satisfied with the result and did not proceed with surgical straightening.

Cons, Complications, and Contraindications

As previously noted, a significant subset of patients will reject the vacuum erection device primarily, and others will discontinue use within the first few months. Common reasons for rejection include perceived cumbersome operation, lack of spontaneity, and partner rejection [20, 81, 82]. Once accepted, vacuum devices are typically well tolerated. Common and rare complications from VCDs are summarized in Table 13.3. Complications tend to be mild and transient, and most commonly include pain or discomfort, numbness, penile bruising, and petechiae. Discomfort may occur during suction in 20–40 % of users, though this tends to improve with familiarization with the device [83]. As many as 45 % of users complain of pain at the constriction ring site [84]. Tight constriction rings can obstruct the urethra leading to painful or failed ejaculation [12, 85]. Erections achieved with VCDs tend to be cool and slightly cyanotic, which may be off-putting to some [17, 83].

There have been anecdotal reports of serious complications from vacuum therapy. Several cases of Peyronie's disease have been reported [86–88]. It is not clear whether the Peyronie's disease is attributable to the device or to increased rigidity and coital activity providing an opportunity to injure the penis, triggering plaque formation in a predisposed individual. In addition, there are single case reports of penile gangrene, Fournier's gangrene, urethral bleeding, and herniation of the scrotal tunica vaginalis into the penile shaft [42, 87, 89]. Physicians should emphasize the 30 min time limit on constriction bands to minimize complications relating to ischemia.

Table 13.3 Complications of vacuum constriction devices

Most common	Rare
Penile discomfort or pain	Peyronie's disease
Ecchymosis/petechiae	Penile hematoma
Difficulty with ejaculation	Penile skin necrosis
Penile cyanosis or coldness	Penile or Fournier's gangrene
Penile numbness	Urethral bleeding

There are no absolute contraindications to VED usage. Relative contraindications include priapism, blood dyscrasias, and penile deformities [42, 85]. Most will cite anticoagulation as a relative contraindication to VED use, though one study shows complication rates in anticoagulated VED users that are comparable to the general population [90]. As previously noted, SCI patients and others with poor sensation are at increased risk of complication. Lack of manual dexterity can complicate device use, though an understanding partner can certainly assist. Cognitive decline can lead to device misuse, which in turn can result in complications [91].

Conclusions and the Future of Vacuum Therapy

Vacuum therapy is a safe, cost-effective, and efficacious erectile aid. It may be used as monotherapy or as adjunctive therapy across all etiologies of erectile dysfunction. Therapy is well tolerated and high satisfaction rates are achieved with those who use VCDs long term. There are very few contraindications to use—nearly any patient with erectile dysfunction is a candidate. The urologic community has only recently begun to explore expanded applications for vacuum therapy including penile rehabilitation, preoperative penile conditioning prior to prosthesis implantation, nonsurgical penile straightening in Peyronie's disease, and even female sexual dysfunction [92]. Given its renewed popularity and expanding domain beyond erectile dysfunction, vacuum therapy may well be on the cusp of an era of innovation.

References

1. Yuan J, Hoang AN, Romero CA, Lin H, Dai Y, Wang R. Vacuum therapy in erectile dysfunction—science and clinical evidence. Int J Impot Res. 2010;22(4): 211–9.
2. Brison D, Seftel A, Sadeghi-Nejad H. The resurgence of the vacuum erection device (VED) for treatment of erectile dysfunction. J Sex Med. 2013;10(4): 1124–35.
3. King J. Contemporary treatment of ED. Indianapolis: Streight and Douglass; 1874. p. 384.
4. Lederer O. Specification of letter patent. US patent No. 1,225,341. Accessed 8 May 1917.
5. Sell FW. Erector. US patent No. 2,874,698. Accessed 24 Feb 1959.
6. Wilson FM. Apparatus for obtaining artificial erection. US patent No. 3,744,486. Accessed 10 July 1973.
7. Geddings D Osbon S, Osbon GD. Erection aid device. US Patent Office. Accessed 29 Mar 1983.
8. Lue TF. Editorial comment on clinical experience of vacuum tumescence enhancement therapy for impotence. J Urol. 1991;145:1112.
9. Montague DK, Barada JH, Belker AM, Levine LA, Nadig PW, Roehrborn CG, et al. Clinical guidelines panel on erectile dysfunction: summary report on the treatment of organic erectile dysfunction. J Urol. 1996;156(6):2007–11.
10. Li E, Hou J, Li D, Wang Y, He J, Zhang J. The mechanism of vacuum constriction devices in penile erection: the NO/cGMP signaling pathway? Med Hypotheses. 2010;75(5):422–4.
11. Nadig PW, Catesby Ware J, Blumoff R. Noninvasive device to produce and maintain an erection-like state. Urology. 1986;27(2):126–31.
12. Witherington R. Vacuum constriction device for management of erectile impotence. J Urol. 1989;141(2):320–2.
13. Sidi AA, Becher EF, Zhang G, Lewis JH. Patient acceptance of and satisfaction with an external negative pressure device for impotence. J Urol. 1990;144(5):1154–6.
14. Cookson MS, Nadig PW. Long term results with vacuum constriction device. J Urol. 1993;149(2):290–4.
15. Segenreich E, Shmuely J, Israilov S, Raz D, Servadio C. Treatment of erectile dysfunction with vacuum constriction device. Harafuah. 1993;124(6): 326–8. 392.
16. Turner LA, Althof SE, Levine SB, Bodner DR, Kursh ED, Resnick MI. External vacuum devices in the treatment of erectile dysfunction: a one-year study of sexual and psychosocial impact. J Sex Marital Ther. 1991;17(2):81–93.
17. Bosshardt RJ, Farwerk R, Sikora R, Sohn M, Jakse G. Objective measurement of the effectiveness, therapeutic success and dynamic mechanisms of the vacuum device. Br J Urol. 1995;75(6):786–91.
18. Kessler WO. Nocturnal penile tumescence. Urol Clin North Am. 1988;15(1):81–6.
19. Vrijhof H, Delaere K. Vacuum constriction devices in erectile dysfunction: acceptance and effectiveness in patients with impotence of organic or mixed aetiology. BJU Int. 1994;74(1):102–5.
20. Dutta TC, Eid JF. Vacuum constriction devices for erectile dysfunction: a long-term, prospective study of patients with mild, moderate, and severe dysfunction. Urology. 1999;54(5):891–3.
21. Meinhardt W, Lycklama a Nijeholt AA, Kropman RF, Zwartendijk J. The negative pressure device for erectile disorders: when does it fail? J Urol. 1993;149(5 Pt 2):1285–7.
22. Mulhall JP. Intracavernosal injection therapy: a practical guide. Tech Urol. 1997;3(3):129–34.
23. Purvis K, Egdetveit I, Christiansen E. Intracavernosal therapy for erectile failure—impact of treatment and reasons for drop-out and dissatisfaction. Int J Impot Res. 1999;11(5):287–99.
24. 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(6):932–5.
25. Avicenna H. The canon of medicine. 1556 ed.
26. Rollo J. Cases of diabetes mellitus. London: C. Dilly; 1798.
27. Thorve VS, Kshirsagar AD, Vyawahare NS, Joshi VS, Ingale KG, Mohite RJ. Diabetes-induced erectile dysfunction: epidemiology, pathophysiology and management. J Diabetes Complications. 2011;25(2):129–36.
28. Lewis RW. Epidemiology of erectile dysfunction. Urol Clin North Am. 2001;28(2):209–16.
29. Price DE, Cooksey G, Jehu D, Bentley S, Hearnshaw JR, Osborn DE. The management of impotence in diabetic men by vacuum tumescence therapy. Diabetic Med. 1991;8(10):964–7.
30. Arauz-Pacheco C, Basco M, Ramirex LC, Pita JM, Pruenda L, Raskin P. Treatment of diabetic impotence with a vacuum device: efficacy and effects on psychological status. Am J Med Sci. 1992;303(5):281.
31. Bodansky HJ. Treatment of male erectile dysfunction using the active vacuum assist device. Diabetic Med. 1994;11(4):410–2.
32. Israilov S, Shmuely J, Niv E, Engelstein D, Livne P, Boniel J. Evaluation of a progressive treatment program for erectile dysfunction in patients with diabetes mellitus. Int J Impot Res. 2005;17(5):431–6.
33. Brown DJ, Hill ST, Baker HWG. Male fertility and sexual function after spinal cord injury. Prog Brain Res. 2006;152:427–39.
34. Linsenmeyer TA. Treatment of erectile dysfunction following spinal cord injury. Curr Urol Rep. 2009;10(6):478–84.
35. Lloyd EE, Toth LL, Perkash I. Vacuum tumescence: an option for spinal cord injured males with erectile dysfunction. SCI Nurs. 1989;6(2):25–8.

36. Zasler ND, Katz PG. Synergist erection system in the management of impotence secondary to spinal cord injury. Arch Phys Med Rehabil. 1989;70(9):712–6.
37. Heller L, Keren O, Aloni R, Davidoff G. An open trial of vacuum penile tumescence: constriction therapy for neurological impotence. Paraplegia. 1992;30(8) :550–3.
38. Denil J, Ohl DA, Smythe C. Vacuum erection device in spinal cord injured men: patient and partner satisfaction. Arch Phys Med Rehabil. 1996;77(8):750–3.
39. Chancellor MB, Hills E, Schwarts M, Hirsch IH. Treatment of erectile dysfunction in males with spinal cord injury using the vacuum constriction device (VCD). J Am Paraplegia Soc. 1991;14:73.
40. Watanabe T, Chancellor MB, Rivas DA, Hirsch IH, Bennett CJ, Finocchiaro MV, et al. Epidemiology of current treatment for sexual dysfunction in spinal cord injured men in the USA model spinal cord injury centers. J Spinal Cord Med. 1996;19(3):186–9.
41. Moemen MN, Fahmy I, AbdelAal M, Kamel I, Mansour M, Arafa MM. Erectile dysfunction in spinal cord-injured men: different treatment options. Int J Impot Res. 2008;20(2):181–7.
42. Rivas DA, Chancellor MB. Complications associated with the use of vacuum constriction devices for erectile dysfunction in the spinal cord injured population. J Am Paraplegia Soc. 1994;17(3):136–9.
43. Chen J, Sofer M, Kaver I, Matzkin H, Greenstein A. Concomitant use of sildenafil and a vacuum entrapment device for the treatment of erectile dysfunction. J Urol. 2004;171(1):292–5.
44. Canguven O, Bailen J, Fredriksson W, Bock D, Burnett AL. Combination of vacuum erection device and PDE5 inhibitors as salvage therapy in PDE5 inhibitor nonresponders with erectile dysfunction. J Sex Med. 2009;6(9):2561–7.
45. Engel JD, Sutherland DE, Williams SB, Wagner KR. Changes in penile length after robot-assisted laparoscopic radical prostatectomy. J Endourol. 2011;25(1):65–9.
46. Basal S, Wambi C, Acikel C, Gupta M, Badani K. Optimal strategy for penile rehabilitation after robot-assisted radical prostatectomy based on preoperative erectile function. BJU Int. 2013;111(4):658–65.
47. John H, Lehmann K, Hauri D. Intraurethral prostaglandin improves quality of vacuum erection therapy. Eur Urol. 1996;29(2):224–6.
48. Cecchi M, Sepich CA, Felipetto R, Vigano L, Pagni G, Minervini R, et al. Vacuum constriction device and topical minoxidil for management of impotence. Arch Esp Urol. 1995;48(10):1058–9.
49. Bellorofonte C, Dell'Acqua S, Mastromarino G, Tombolini P, Ruoppolo M, Zaatar C. External devices: for which patients? Arch Ital Urol Androl. 1995;67(5):293–8.
50. Soderdahl DW, Petroski RA, Mode D, Schwartz BF, Thrasher JB. The use of an external vacuum device to augment a penile prosthesis. Tech Urol. 1996;3(2):100–2.
51. Korenman SG, Viosca SP. Use of a vacuum tumescence device in the management of impotence in men with a history of penile implant or severe pelvic disease. J Am Geriatr Soc. 1992;40(1):61–4.
52. Wylie KR, Jones RH, Walters S. The potential benefit of vacuum devices augmenting psychosexual therapy for erectile dysfunction: a randomized controlled trial. J Sex Marital Ther. 2003;29(3):227–36.
53. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med. 2009;6(9):2538–46.
54. Alemozaffar M, Regan MM, Cooperberg MR, Wei JT, Michalski JM, Sandler HM, et al. Prediction of erectile function following treatment for prostate cancer. JAMA. 2011;306(11):1205–14.
55. Burnett AL. Erectile dysfunction following radical prostatectomy. JAMA. 2005;293(21):2648–53.
56. Meyer JP, Gillatt DA, Lockyer R, Macdonagh R. The effect of erectile dysfunction on the quality of life of men after radical prostatectomy. BJU Int. 2003;92(9):929–31.
57. Penson DF, Feng Z, Kuniyuki A, McClerran D, Albertsen PC, Deapen D, et al. General quality of life 2 years following treatment for prostate cancer: what influences outcomes? Results from the prostate cancer outcomes study. J Clin Oncol. 2003;21(6):1147–54.
58. Leungwattanakij S, Bivalacqua TJ, Usta MF, Yang D-Y, Hyun J-S, Champion HC, et al. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. J Androl. 2003;24(2):239–45.
59. Mulhall JP, Bella AJ, Briganti A, McCullough A, Brock G. Erectile function rehabilitation in the radical prostatectomy patient. J Sex Med. 2010;7(4 Pt 2):1687–98.
60. Kim JH, Lee SW. Current status of penile rehabilitation after radical prostatectomy. Korean J Urol. 2015;56(2):99–108.
61. Fraiman M, Lepor H, McCullough A. Changes in penile morphometrics in men with erectile dysfunction after nerve-sparing radical retropubic prostatectomy. Mol Urol. 1999;3(2):109–15.
62. Gontero P, Galzerano M, Bartoletti R, Magnani C, Tizzani A, Frea B, et al. New insights into the pathogenesis of penile shortening after radical prostatectomy and the role of postoperative sexual function. J Urol. 2007;178(2):602–7.
63. Munding MD, Wessells HB, Dalkin BL. Pilot study of changes in stretched penile length 3 months after radical retropubic prostatectomy. Urology. 2001;58(4):567–9.
64. Vasdev N, Hoyland K, Adshead JM. Is it still clinically and economically viable in the UK to prescribe vacuum erection devices for patients with erectile dysfunction after radical prostatectomy? BJU Int. 2014;113(3):356–7.
65. Tal R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. J Sex Med. 2011;8(8):2370–6.

66. Kirby M. Best practice guidelines on the use of vacuum constriction devices for erectile dysfunction following radical prostatectomy. Br Soc Sexual Med. 2011.
67. Broderick GA, McGahan JP, Stone AR, White RD. The hemodynamics of vacuum constriction erections: assessment by color Doppler ultrasound. J Urol. 1992;147(1):57–61.
68. Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, Montague DK, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. Int J Impot Res. 2006;18(1):77–81.
69. Dalkin BL, Christopher BA. Preservation of penile length after radical prostatectomy: early intervention with a vacuum erection device. Int J Impot Res. 2007;19(5):501–4.
70. Köhler TS, Pedro R, Hendlin K, Utz W, Ugarte R, Reddy P, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU Int. 2007;100(4):858–62.
71. Fode M, Ohl DA, Ralph D, Sønksen J. Penile rehabilitation after radical prostatectomy: what the evidence really says. BJU Int. 2013;112(7):998–1008.
72. 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(1):58–62.
73. Gontero P, Fontana F, Zitella A, Montorsi F, Frea B. A prospective evaluation of efficacy and compliance with a multistep treatment approach for erectile dysfunction in patients after non-nerve sparing radical prostatectomy. BJU Int. 2005;95(3):359–65.
74. Aghamir MK, Hosseini R, Alizadeh F. A vacuum device for penile elongation: fact or fiction? BJU Int. 2006;97(4):777–8.
75. Moskovic DJ, Pastuszak AW, Lipshultz LI, Khera M. Revision of penile prosthesis surgery after use of penile traction therapy to increase erect penile length: case report and review of the literature. J Sex Med. 2011;8(2):607–11.
76. Sellers T, Dineen M, Wilson SK. Vacuum protocol and cylinders that lengthen allow implantation of longer inflatable prostheses reducing complaints of shortened penile length. J Urol. 2009;181(4):449.
77. Sellers T, Dineen M, Salem EA, Wilson SK. Vacuum preparation, optimization of cylinder length and postoperative daily inflation reduces complaints of shortened penile length following implantation of inflatable penile prosthesis. ASM. 2013;2013(01):14–8.
78. Moul JW, McLeod DG. Negative pressure devices in the explanted penile prosthesis population. J Urol. 1989;142(3):729–31.
79. Chung E, Brock G. Penile traction therapy and Peyronie's disease: a state of art review of the current literature. Ther Adv Urol. 2013;5(1):59–65.
80. Raheem AA, Garaffa G, Raheem TA, Dixon M, Kayes A, Christopher N, et al. The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. BJU Int. 2010;106(8):1178–80.
81. Derouet H, Caspari D, Rohde V, Rommel G, Ziegler M. Treatment of erectile dysfunction with external vacuum devices. Andrologia. 1999;31(S1):89–94.
82. Althof SE, Turner LA, Levine SB, Bodner D, Kursh ED, Resnick MI. Through the eyes of women: the sexual and psychological responses of women to their partner's treatment with self-injection or external vacuum therapy. J Urol. 1992;147(4):1024–7.
83. Levine LA, Dimitriou RJ. Vacuum constriction and external erection devices in erectile dysfunction. Urol Clin North Am. 2001;28(2):335–42.
84. Oakley N, Moore KT. Vacuum devices in erectile dysfunction: indications and efficacy. Br J Urol. 1998;82(5):673–81.
85. Lewis RW, Witherington R. External vacuum therapy for erectile dysfunction: use and results. World J Urol. 1997;15(1):78–82.
86. Hakim LS, Munarriz RM, Kulaksizoglu H, Nehra A, Udelson D, Goldstein I. Vacuum erection associated impotence and Peyronie's disease. J Urol. 1996;155(2):534–5.
87. Ganem JP, Lucey DT, Janosko EO, Carson CC. Unusual complications of the vacuum erection device. Urology. 1998;51(4):627–31.
88. Kim 3rd JH, Carson CC. Development of Peyronie's disease with the use of a vacuum constriction device. J Urol. 1993;149(5 Pt 2):1314–5.
89. Theiss M, Hofmockel G, Frohmuller HGW. Fournier's gangrene in a patient with erectile dysfunction following use of a mechanical erection aid device. J Urol. 1995;153(6):1921–2.
90. Limoge JP, Olins E, Henderson D, Donatucci CF. Minimally invasive therapies in the treatment of erectile dysfunction in anticoagulated cases: a study of satisfaction and safety. J Urol. 1996;155(4):1276–9.
91. Bratton RL, Cassidy HD. Vacuum erection device use in elderly men: a possible severe complication. J Am Board Fam Pract. 2002;15(6):501–2.
92. Billups KL. The role of mechanical devices in treating female sexual dysfunction and enhancing the female sexual response. World J Urol. 2002;20(2):137–41.
93. Blackard CE, Borkon WD, Lima JS, Nelson J. Use of vacuum tumescence device for impotence secondary to venous leakage. Urology. 1993;41(3):225–30.
94. Baltaci S, Aydos K, Kosar A, Anafarta K. Treating erectile dysfunction with a vacuum tumescence device: a retrospective analysis of acceptance and satisfaction. BJU Int. 1995;76(6):757–60.
95. Kolettis PN, Lakin MM, Montague DK, Ingleright BJ, Ausmundson S. Efficacy of the vacuum constriction device in patients with corporeal venous occlusive dysfunction. Urology. 1995;46(6):856–8.

14 Self-Injection, Transurethral, and Topical Therapy in Erectile Dysfunction

Cynthia L. Bednarchik, Michael Kottwitz, and Scott W. Geiger

Introduction

Currently there are three main therapeutic agents for intracavernosal injection (ICI) therapy and one for intraurethral therapy approved by the FDA for the treatment of erectile dysfunction (ED). These agents are highly effective and were the focus of intense interest in the mid-1990s, but were quickly regulated to second line therapy after the appearance of sildenafil. Indeed, while sildenafil prescriptions nearly doubled to 14 million from 1998 to 2001, prescriptions for alprostadil injections dropped by one third to 159,000 and MUSE® (Meda Pharmaceuticals, Inc., Somerset NJ) prescriptions fell by two thirds to 132,000 [1]. It must be noted, however, that the phosphodiesterase-5 inhibitors (PDE5Is) are ineffective in about 22–35 % of men [2]. Furthermore, of the men treated with oral agents, a significant proportion will ultimately fail (even after PDE5I dose escalation) secondary to progression of their disease. Additionally, there are a significant number of men with contraindications to PDE5Is. The result is a large number of men who are unable to utilize oral treatments for erectile dysfunction. Fortunately, second line therapies in the form of vacuum erection devices (discussed in detail in a separate chapter: Chap. 13), ICI, and MUSE® are highly effective treatments that may be used when PDE5Is are contraindicated. Interestingly, there is also a significant subset of men who prefer intracavernous injection to PDE5I therapy, even when both are effective. Hatzichristou et al. [3] tested the efficacy of sildenafil in 155 men who were using intracavernous injections and obtaining successful results. Seventy-five percent (116) of those men achieved erections sufficient for intercourse. Of those 116 men in whom both treatments were successful, 33 % (38 men) chose to continue intracavernous injection therapy instead of switching to oral medications. In short, despite being overshadowed by the mass marketing and convenience of administration of PDE5Is, knowledge and utilization of ICI and MUSE® remain critical in the approach to treatment of erectile dysfunction.

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PGE_1 (Alprostadil)

Alprostadil acts via multiple pathways to cause cavernosal vascular smooth muscle relaxation and thus erection. The best characterized of these

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pathways is via increase in cAMP, which results in increased activity of cAMP dependent kinases, thus decreased cytoplasmic Ca^{2+}, and relaxation of smooth muscle [4]. Other less well characterized pathways including cAMP mediated increases in cGMP and the indirect blockade of adrenergic and angiotensin II signaling by PGE_1 [5, 6], are also likely to play a role. The mechanism is illustrated in Fig. 14.1.

Prostaglandin E_1 is now the preferred injectable agent and only transurethral erectile agent. Trade names for the injectable form are Caverject® (Pfizer Inc., New York, NY) and Edex® (Auxilium Inc/Endo, Dublin, Ireland)/Viridal® (UCB Pharma, Brussels, Belgium). Generic injectable alprostadil is also available and typically is more cost effective, but does not include a sophisticated delivery system as described below. MUSE® (Medicated Urethral System for Erection, Meda Pharmaceuticals) is currently the only transurethral erectile agent approved by the FDA. Typical doses are 10–20 μg for injectable alprostadil and 250–1000 μg for MUSE® alprostadil.

Response rates to alprostadil alone are high. In his 1996 meta-analysis [7], Porst reported a 70 % rate of erection sufficient for intercourse with alprostadil injection alone in greater than 10,000 patients (Table 14.1). This included 4500 patients from his own series and more than 5000 from a literature review. A later publication by Porst [8] reported on 162 patients using alprostadil ICI, 58 of which were followed for 4 years for a total of 16,886 injections. Success rates were greater than 90 % in each year of the study (Table 14.2).

Perhaps more important than generalized efficacy is efficacy in PDE5I nonresponders. Shabsigh et al. [9] reported on 67 patients with no response to PDE5Is. Of these, 59 (88 %) reported achieving erections suitable for intercourse using ICI. Nagai et al. [10] reported a similar study, which tested the efficacy of intracavernous alprostadil on 64 patients who failed PDE5I therapy. Ninety-one percent of these patients achieved erections suitable for intercourse with ICI alprostadil therapy.

Interestingly, the converse is also sometimes true and approximately a third of patients who do not respond to intracavernous therapy respond to PDE5Is. McMahon et al. [11] challenged 93 men with ED who previously failed ICI with oral sildenafil, 50 mg, escalating to 100 mg if the low dose was unsuccessful and found that 34 % achieved erections suitable for intercourse. Thirty of these 32 required the 100 mg dose of sildenafil.

Administration

Caverject® comes in two forms: a vial containing powdered alprostadil and a prefilled dialable syringe (Caverject®Impulse®). The first type comes in doses of 5, 10, and 20 μg and requires premixing with a diluent, which is either bacteriostatic water or simply sterile water. The injection site is selected as per Fig. 14.2. The penis is

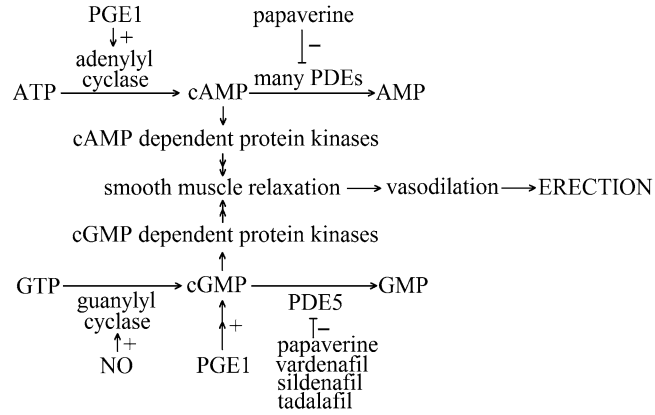

Fig. 14.1 Mechanism of action in producing erections for alprostadil (PGE1), papaverine, and the PDE-5 inhibitors

Table 14.1 Response rates to PGE_1, papaverine, and papaverine + phentolamine

Drug	Total # patients	Dosage	Responders
PGE_1			
Literature review	10,353	5–40 μg	7519/10,353 (72.6 %)
Porst series	4577	5–20 μg	3206/4577 (70 %)
Papaverine			
Literature review	2161	30–110 mg	987/1611 (61 %)
Porst series	950	12.5–50 mg	370/950 (39 %)
Papaverine + phentolamine			
Literature review	3016	15 mg + 1.25 mg	2065/3016 (68.5 %)
		60 mg + 2 mg	
Porst series	249	15 mg + 1 mg	151/249 (60.6 %)
		50 mg + 2 mg	

Used with permission from Porst H., The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urol 1996;155(3): 802–15

Table 14.2 Success rates for alprostadil ICI over 4 years

Year	#Patients	# Injections	Successful coitus (%)
1	162	6935	6293 (90.7)
2	81	3937	3691 (93.8)
3	68	3233	3050 (94.3)
4	58	2781	2679 (96.3)

Used with permission from Porst H et al. Intracavernous Alprostadil Alfadex--an effective and well tolerated treatment for erectile dysfunction. Results of a long-term European study. Int J Impot Res 1998; 10(4): 225–31

grasped by the glans and stretched against one thigh. The site is cleaned with an alcohol swab and the solution is injected into the corpus cavernosum as per Fig. 14.3. Care is taken to avoid the neurovascular structures on the dorsum of the penis and the corpus spongiosum on the ventral side of the penis. Pressure should be applied to the injection site for 5 min to prevent hematoma formation. The patient is instructed to alternate sites [12].

Caverject® Impulse® is available in two strengths, 10 and 20 μg. Administration is similar except that both the diluent and the drug are present in the same syringe, and mixing is accomplished by turning the plunger rod. The patient's dose is then dialed in on the syringe and the drug is injected in the same fashion as the original drug. The package insert diagram of the syringe is shown in Fig. 14.4 [13].

Edex® is a system somewhat similar to Caverject® Impulse. It consists of a reusable injection device with single use and dual chambered medication cartridges. The system is shown in Fig. 14.5 [14].

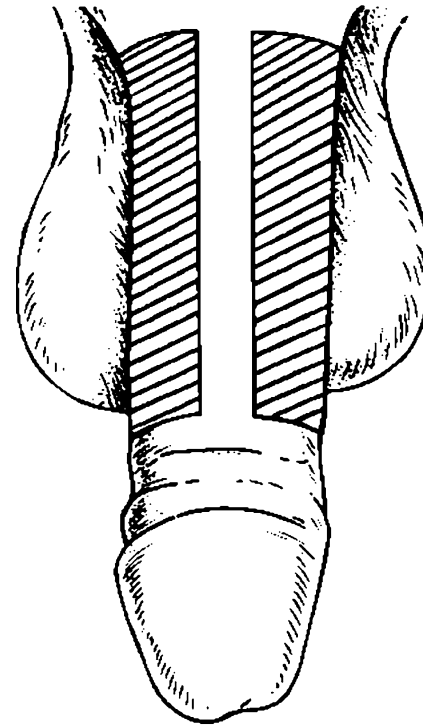

Fig. 14.2 Penile injection site. Shaded areas represent ideal injection sites for ICI (From Caverject® Package Insert. Used with permission. Copyright © Pfizer Inc., New York, NY)

The cartridge is inserted into the injection device and the plunger is depressed to add the diluent to the medication. The medication is

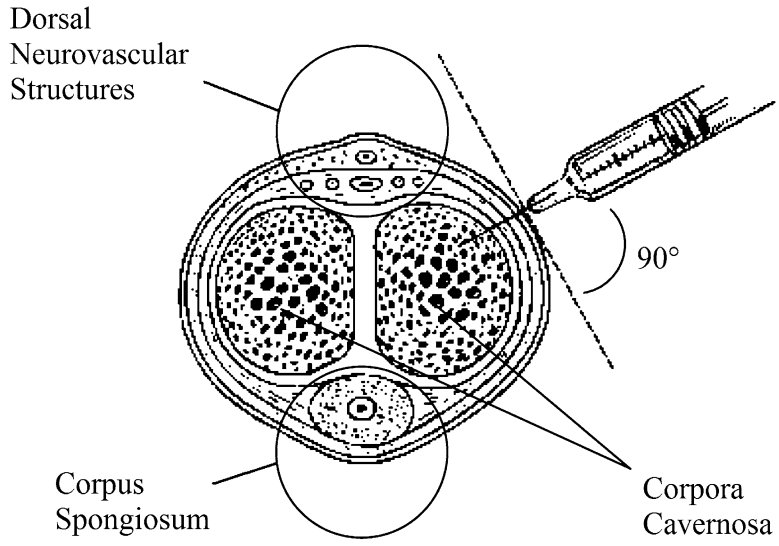

Fig. 14.3 Avoid injection into important dorsal and ventral penile structures (From Caverject® Package Insert. Used with permission. Copyright © Pfizer Inc., New York, NY)

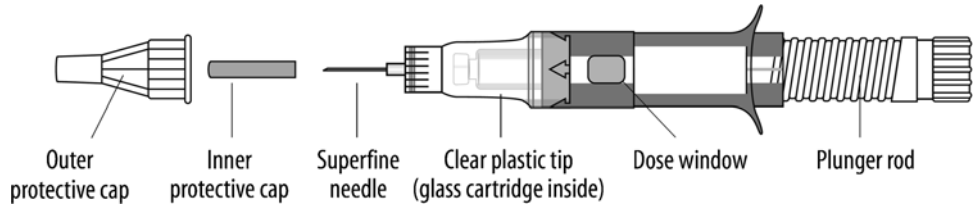

Fig. 14.4 Caverject® Impulse® syringe (From Caverject® Impulse® Package Insert. Used with permission. Copyright © Pfizer Inc., New York, NY)

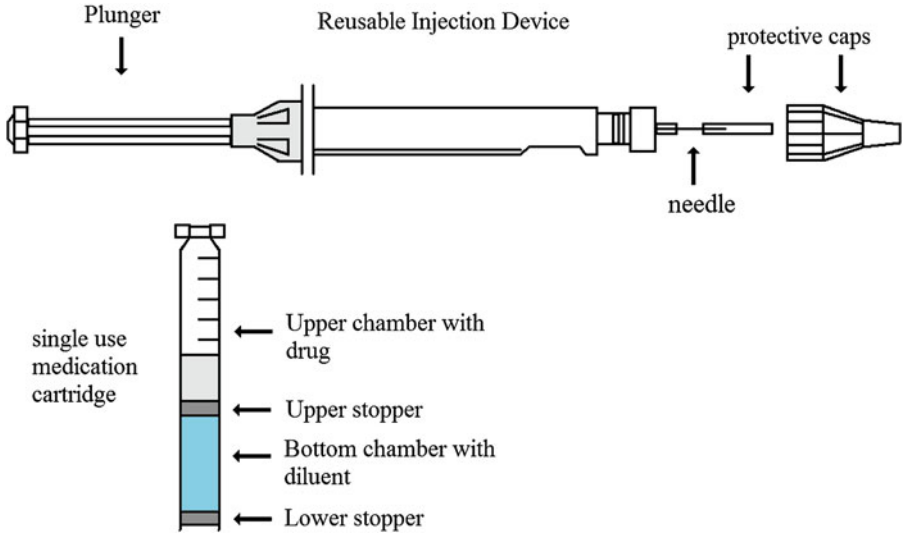

Fig. 14.5 Edex® cartridge and injection device diagrams (From Edex® package Insert. Used with permission. Copyright © Endo/Auxilium Pharmaceuticals Inc., Dublin, Ireland)

Table 14.3 Complications of ICI therapy: alprostadil, papaverine, and bimix

Drug	Total # patients	Priapism >6 h (%)	Nodules, indurations, fibrosis (%)	Pain (%)	Hematoma (%)
Alprostadil	2745	0.36	0.8	7.2	6.6
Bimix	2263	7.8	12.4	11.6	25.6
Papaverine	1527	7.1	5.7	4.0	11.4

Used with permission from Porst H., The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urol 1996;155(3): 802–15

then swirled into the diluent and injected into the penis as per the above directions for Caverject®.

Generic alprostadil is available in powdered vials that require mixing with diluent and are administered as per the directions for Caverject®. Premixed generic alprostadil can also be obtained from specialized pharmacies. Recommended needle size is ½ in., 27–30 gauge.

Side Effects

Penile pain is the most significant side effect of alprostadil. In his 1996 literature review [7], Porst describes the experience of 2745 patients over ten publications (Table 14.3). He notes that the rate of penile pain with ICI alprostadil is 7.2 %. Higher rates of pain are noted by the European Alprostadil Study Group [15]. They noted that 44 % of their 848 patients experienced penile pain, but this was described as mild in over half of those patients and only 3 % discontinued because of pain. Smaller studies note intermediate outcomes [16]. Priapism and fibrosis occurred at low rates of 0.36 and 0.8 % [7]. The European Alprostadil Study Group [15] notes 0.9 and 4 % rates for those same phenomena.

Alprostadil Summary Points

- Alprostadil ICI is highly efficacious (>70 %) in producing erections.
- In patients who fail PDE5 inhibitors, efficacy is ~90 %.
- This is the most commonly used ICI agent. It is FDA approved and is available at most pharmacies.
- The most significant side effect of pain occurs at a rate of ~7 % of patients. Higher rates of up to 40 % are sometimes reported, but this is likely due to the inclusion of minor pain. It is popularly thought to have the highest rates of penile pain of all the ICI agents; however, this is not borne out in the literature.
- Rates of serious side effects of priapism and fibrosis are low.

Papaverine

Papaverine acts as a nonspecific phosphodiesterase inhibitor to block both the breakdown of cAMP and cGMP, the accumulation of both of which leads to decreased intracellular calcium and thus smooth muscle relaxation [17]. The mechanism of action is illustrated in Fig. 14.1.

Papaverine was the first agent discovered to be effective as intracavernous pharmacotherapy for erectile dysfunction [18]. It is highly effective, but has fallen out of favor as monotherapy because of its high rates of fibrosis. Rates of success are between 60 and 93 % [19–23], though some of these studies use very high doses of papaverine. Up to 120 mg of papaverine was used in Brindley's series of 73 patients. Porst's literature review [7] (Table 14.1) revealed 987 responders of 1611 subjects (61 %) for dosages ranging from 30 to 110 mg. His personal series of 950 patients showed a more modest response rate of 39 % (390 responders) at more commonly used doses ranging from 12.5 to 50 mg.

Administration

Papaverine is obtained only as a generic medication in the USA. In Europe, it is approved and marketed as Androskat. It comes in 2 and 10 mL vials of papaverine 30 mg/mL solution. Typical doses range from 30 to 60 mg. It is and injected in the same fashion as Caverject®.

Side Effects

Virag et al. [24] reported one of the largest series of patients using papaverine ICI for erectile dysfunction. In this series, 163,042 papaverine injections were administered to 1748 patients. The main side effects noted were priapism and fibrosis. Priapism occurred in 106 (6 %) of patients after 235 (0.14 %) of the injections. Fibrosis or nodule formation occurred in 187 (11 %) of patients.

A literature review by Porst [7] which did not include the above study by Virag et al. revealed slightly different rates. Priapism was noted in 92 (7 %) of 1300 patients. Fibrosis, induration, and nodules occurred in 5.7 % (60 of 1056 patients) in the literature review. Other important side effects were injection site pain, which occurred in 4 % (18/452 patients), and hematoma, which occurred in 11 % (98/858 patients). Elevated liver enzymes, commonly seen with oral papaverine use [25], was seen in 1.6 % (5/314) of patients using intracavernosal papaverine.

Papaverine Summary Points

- Papaverine is efficacious (39–61 %); however, its high rate of serious side effects, priapism, and fibrosis, at the high doses often needed for solitary use make its use unattractive.
- Both efficacy and side effects are likely dose dependent.

Phentolamine

Alpha-blockers inhibit smooth muscle contraction in the corpora by, as the class name implies, inhibiting alpha-adrenergic receptors. The main alpha-blockers used for erectile dysfunction are phentolamine and moxisylyte. Moxisylyte was available in Europe as Icavex, but was withdrawn in 2005. Currently, only phentolamine is widely used for erectile dysfunction.

Phentolamine has poor efficacy as a solo drug for erectile dysfunction. This stems from the fact that phentolamine induces tumescence relatively poorly, but instead it is more effective in countering the body's intrinsic cascade to induce detumescence by blocking the effects on norepinephrine. In a small study on eight impotent patients and two normal controls, Blum et al. [26] noted that the control patients achieved full erections, but that the impotent patients achieved only tumescence, not full erections.

Side Effects

Since phentolamine is almost universally ,used in conjunction with papaverine and alprostadil, data on its side effects as a solo therapy for erectile dysfunction are not adequately reported.

Intracavernous Injection Combinations

Combination therapy for intracavernous injections was conceived to improve efficacy as a result of the synergistic effects of the drugs, and later, to reduce side effects as a result of using lower dosages of each agent.

One difficulty encountered with the use of combination agents is the need for the pharmacy to compound these agents since there are no combination intracavernous injection drugs currently approved by the FDA. In Europe, bimix is approved in several countries. Besides the obvious logistical difficulties in obtaining the medications, it also then becomes necessary for the patient to use combinations containing alprostadil with some degree of expediency. This is due to the degradation of alprostadil in solution which occurs at a rate of approximately 30 % over the course of 2 months [27].

Bimix (Papaverine, Phentolamine)

The combination of papaverine and phentolamine is attractive since it is highly effective. No FDA approved combination exists. In Europe, a papaverine–phentolamine combination is marketed as Androskat. It is distributed as a 2 mL ampule of papaverine 15 mg/mL and phentolamine 0.5 mg/mL.

The combination of papaverine and phentolamine is seen as an alternative to alprostadil monotherapy when significant pain results from alprostadil injection. Unfortunately, bimix also results in significant pain in a large percentage of patients using it, though the populations experiencing pain from the two regimens do not necessarily overlap.

Efficacy of bimix in Porst's literature review [7] is shown in Table 14.1. It should be noted that bimix and alprostadil have nearly equivocal efficacies at 68.5 and 73 %, respectively. The approximate dose equivalency of 10 μg of alprostadil has similar efficacy to 30 mg papaverine + 1 mg phentolamine.

Trimix (PGE_1, Papaverine, Phentolamine)

No standardized mixture is approved by the FDA or any European regulatory agencies and so these must be compounded by the pharmacy based on physician instructions. Concentrations of each component vary widely in the literature, but ratios of 12–30 mg papaverine–10–20 μg alprostadil–1 mg phentolamine are fairly standard. Albaugh [28] recommends a mixture of 30 mg papaverine + 10 μg alprostadil + 1 mg phentolamine per 1 mL with a starting dose of 0.1–0.5 mL.

Bechara et al. [29] reported a crossover study of alprostadil vs. trimix in a group of 32 men who had failed high dose bimix therapy. In this study, 50 % responded to trimix compared to only 22 % responding to alprostadil. Rates of pain for alprostadil were significantly higher than for trimix (41 % vs. 12.5 %).

Seyam et al. [30] studied multiple combinations of trimix ingredients vs. alprostadil in 180 men with erectile dysfunction. They found that all tested mixtures were highly effective and produce erections that are of equal frequency and quality to those produced by alprostadil. Sixty-eight percent of men using alprostadil and 67 % of men using trimix achieved a rigid erection. However, duration of erections is longer than alprostadil and a larger number of episodes of priapism (5 % vs. 0.6 %) were produced. Interestingly, rates of pain were similar between the combined trimix group and the alprostadil group (14.5 % vs. 17.9 %, respectively).

Combining trimix with sildenafil increases efficacy even in patients who are recalcitrant to many other pharmaceutical therapies. McMahon et al. [11] found that of 62 patients who failed high dose sildenafil, high dose alprostadil, and high dose trimix separately, 29 (47.5 %) achieved erections sufficient for intercourse by combining trimix with oral sildenafil. Trimix concentration used in this study was 24 mg papaverine + 20 μg alprostadil + 1.6 mg phentolamine per 1 mL with a mean dose of 0.6 mL and a dose range from 0.15 mL to 1 mL.

Limited data exist about the potential for trimix to cause fibrosis. One study [31] reported 2 (3.8 %) episodes of clinically evident fibrosis of 53 patients using trimix. Few studies report data on fibrosis. While it is important to know that fibrosis can occur on trimix, stated rates of occurrence are misleading as there is no standard ratio, dose, or recommended frequency of trimix administration, and fibrosis is likely a phenomenon related to dose of phentolamine.

Dose equivalence data comparing alprostadil to trimix were published by Kulaksizoglu et al. [32]. Table 14.4 demonstrates their findings.

Quadmix (PGE_1, Papaverine, Phentolamine, Atropine)

Minimal data exist about this mixture. Sogari et al. [33] randomized 230 men to office tests of trimix vs. quadmix and found no significant difference between the two. Both resulted in full erection in 52 of the 114 in their respective groups.

Table 14.4 Dose equivalence of alprostadil and a trimix mixture

Alprostadil powder (μg)	Papaverine (mg)–phentolamine (mg)–alprostadil (μg)
4	1.47/0.05/0.49
8	3.2/0.1/1.1
12	4.6/0.15/1.55
16	6.8/0.22/2.27
20	7.6/0.25/2.5

Used with permission from Kulaksizoglu H, Hakim LS, Nehra A, Goldstein I. Comparison of alprostadil sterile powder (Caverject®) with trimix. Nomogram and patient satisfaction. J Urol. 1997;157(Suppl 4):180

ICI Combination Summary Points

- These are not FDA approved and thus must be compounded in the pharmacy, limiting their availability and use.
- Bimix (papaverine–phentolamine) was a popular combination. It is highly efficacious, but, like solo papaverine, is now infrequently used due to the high incidence of priapism and fibrosis. Currently, it is used when even small amounts of alprostadil result in penile pain necessitating its removal from the injection combination.
- Trimix (papaverine–phentolamine–alprostadil) is commonly used if alprostadil monotherapy produces excessive pain. The lower effective doses of each component limit the side effects while maintaining efficacy; it is at least as efficacious as alprostadil.
- Efficacy and side effect rates of trimix are highly variable and related to the concentration, doses, and frequency of its components.

Selection of Injectable Agents

Though all aforementioned agents are available, the small but real risk of significant permanent side effects of papaverine generally precludes its use, alone or with phentolamine, as an initial agent. This leaves only alprostadil and trimix as initial agents, both of which are appropriate choices. Generally alprostadil is chosen as a first line therapy given its low risk of priapism and fibrosis. Trimix may be used as an initial agent if alprostadil is cost prohibitive and a compounding pharmacy is available. Recommended starting doses for alprostadil and trimix are dependent on age and history of previous radical prostatectomy [28]. An algorithm to help select an intracavernous agent is shown in Fig. 14.6.

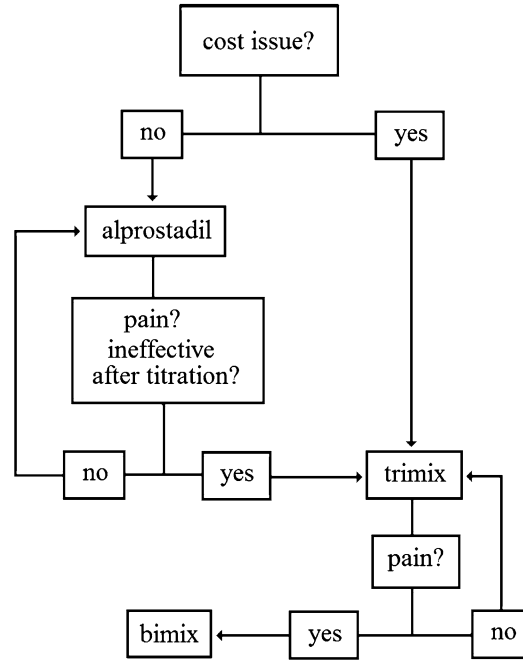

Fig. 14.6 Selecting an intracavernous injection agent (Reprinted from Albaugh JA. Intracavernosal injection algorithm. Urol Nurs 2006; 26(6): 449–53. Used with permission of the publisher, The Society of Urologic Nurses and Associates, Inc. (SUNA), East Holly Avenue, Box 56, Pitman, NJ 08071-0056; Phone: 856-256-2300; Fax: 856-589-7463; e-mail: uronsg@ajj.com; Website: www.suna.org. For a sample copy of the journal, please contact the publisher)

The package insert for Caverject® recommends a 2.5 μg starting dose, with an optional second dose of 2.5 μg if the first dose is unsuccessful. Thereafter, titration may proceed by 5–10 μg steps. These increases after the first two doses should be at least 24 h apart. Albaugh notes that initial doses of 5 and 10 μg are common in the literature and suggests starting with 5 μg if the patient is less than 65 or has had a radical prostatectomy in the past 2 years. If the man is younger than 55 and has had a prostatectomy in the past 2 years, the dose should be reduced to 2.5 μg. If the man is greater than 65 and has not had a radical prostatectomy in the past 2 years, the initial dose may be increased to 10 μg.

Table 14.5 Representative prices of different ICI prices from one pharmacy

Formula	Volume (mL)	Papaverine (mg/mL)	Phentolamine (mg/mL)	Alprostadil (μg/mL)	Price range ($)
Trimix #1	10	16.7	0.56	5.6	55–70
Trimix #2	10	30	1	10	70–85
Trimix #3	8.25	21.8	1.21	15	60–80
Trimix #4	14.4	20.8	1.4	14	120–150
Trimix #5	12.5	24	0.8	20	80–110
Alprostadil #1	12.5	–	–	20	55–70
Alprostadil #2	12.5	–	–	40	55–75
Bimix	12.5	30	2	–	70–80

Data from Pharmacy Creations, R., New Jersey, Erectile Dysfunction Compounds Price List. Received September 16, 2008

Given the wide range of trimix mixtures, there are no standard recommendations on starting doses, as such, tailoring of mixtures and starting doses is the norm. As a starting point, the recommendations from Albaugh are as follows. A mixture of alprostadil 10 μg, phentolamine 1 mg, and papaverine 30 mg per mL is used. Starting doses are 0.1–0.2 mL for patients less than 60 years old who are less than 2 years post-prostatectomy. A higher dose of 0.3 mL is used in all other patients.

If pain or cost is a significant issue with alprostadil use (relevant in nongeneric formulations), switching to trimix is recommended. If pain remains an issue with trimix, a subsequent change to bimix is recommended. Table 14.5 lists prices for generic alprostadil, bimix, and trimix from one pharmacy [34].

Contraindications to ICI

Intracavernous injections should not be used in men with conditions, which predispose them to priapism. These notably include men with sickle-cell disease, multiple myeloma, and leukemia. They should also not be used in conditions, which cause penile angulation such as Peyronie's or cavernosal fibrosis [12]. Also, they should not be used for patients in whom sexual activity is unadvisable.

Anticoagulation is not a contraindication to ICI. In a series of 605 injections in 33 men using warfarin for anticoagulation, Limoge et al. [35] recorded only three ecchymoses. This rate of 9 % of patients is comparable to the 14 % (434/3143) of patients on PGE_1, papaverine, or bimix who developed hematoma in Porst's literature review [7]. Despite this, it is advisable that the physician stresses the need, in anticoagulated patients, to place pressure on the injection site for five full, uninterrupted minutes of pressure to prevent hematoma.

Management of Side Effects

Patients must be made aware of the risk of priapism that occurs with ICI, particularly papaverine ICI, use and educated about the proper course of action to take should they experience a prolonged erection. Sympathomimetic drugs, namely pseudoephedrine and terbutaline, are commonly prescribed or recommended to patients as a way of aiding detumescence in cases of prolonged erection and priapism. Some evidence exists to support their use. Lowe and Jarow [36] tested the use of terbutaline, pseudoephedrine, and placebo (sodium bicarbonate) in 75 men with prolonged erections due to alprostadil ICI. Both terbutaline and pseudoephedrine performed better than placebo, with detumescence resulting in 36, 28 and 12 % respectively. Only the difference between terbutaline and placebo achieved statistical significance. Notable in this study, oral terbutaline or pseudoephedrine only worked in a third of patients. The other two thirds

required irrigation and/or phenylephrine injections. None required surgical intervention. A study by Priyadarshi [37] showing detumescence in 42 % of patients with ICI induced priapism compared with 15 % detumescence with placebo in 68 men confirms the efficacy of terbutaline. Consequently, prescription for two tablets of terbutaline 5 mg is a common practice. The patient is instructed to take one, and if detumescence has not occurred, to take the second after 15 min.

Cavernosal fibrosis is another serious side effect of intracavernosal injections. It occurs most commonly with injectables containing papaverine. Rates are less than one percent with alprostadil, approximately 6 % with papaverine, and around 12 % with bimix. Rates with trimix were 4 % in a small study. These are likely dependent on dose and frequency of use. There is no treatment to reverse penile fibrosis, though it sometimes regresses on its own. Tsao and Nehra [38] recommend temporary discontinuation of ICI for 3–4 months to allow resolution. Persistence of fibrosis should prompt a change to more invasive methods of improving erectile function, i.e., placing a penile prosthesis.

Pain is a significant side effect, especially in a drug whose sole purpose is improvement in quality of life. Pain, coupled with the psychological aspects of injection of the penis can be seen as a fatal flaw of intracavernous injection. Reported rates of pain with injection are 7 % for alprostadil, 4 % with papaverine, 12 % with bimix [7], and 12–15 % with trimix [29, 30]. Significantly, it has been observed that pain decreases substantially during the course of treatment [13], so it is likely that the psychological component plays a large role. Albaugh and Ferrans [39] reported a study on pain with intracavernosal injection. They separated the pain into needle pain and medication pain, both measured on a scale of 0–10 with 10 being the worst imaginable pain. Findings are represented in Figs. 14.7 and 14.8.

Two other important results of this study were that only 4 of 65 patients reported that they would discontinue ICI as a result of pain, and pain was significantly higher in post-prostatectomy patients (52 % vs. 24 %). As stated previously, of patients in whom both PDE5Is and ICI are effective, one third will choose ICI [3]. Given this and the findings of Albaugh and Ferrans, patients seeking highly efficacious ED treatment can be counseled to try ICI with the assurance that most men have very minimal to no pain.

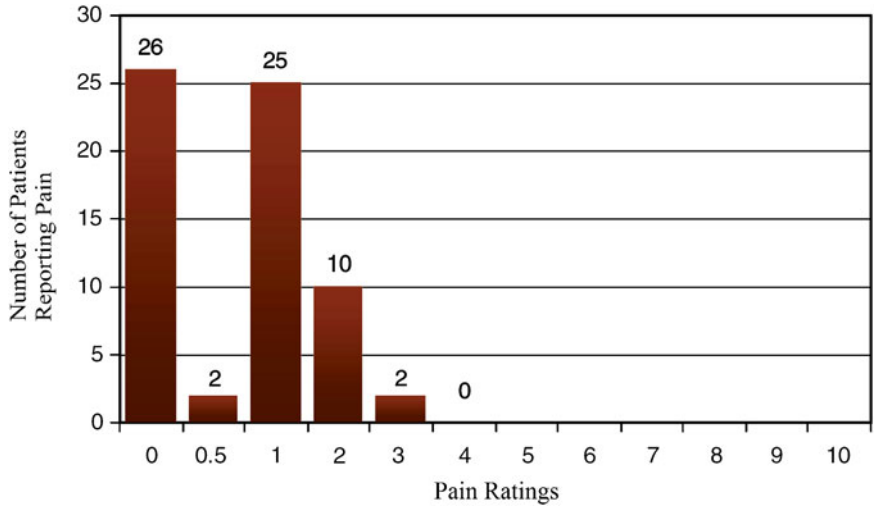

Fig. 14.7 Needle induced pain in ICI (Used with permission of Albaugh J, Ferrans DE. Patient-reported pain with initial intracavernosal injection. J Sex Med, 2009; 6(2): 513–9)

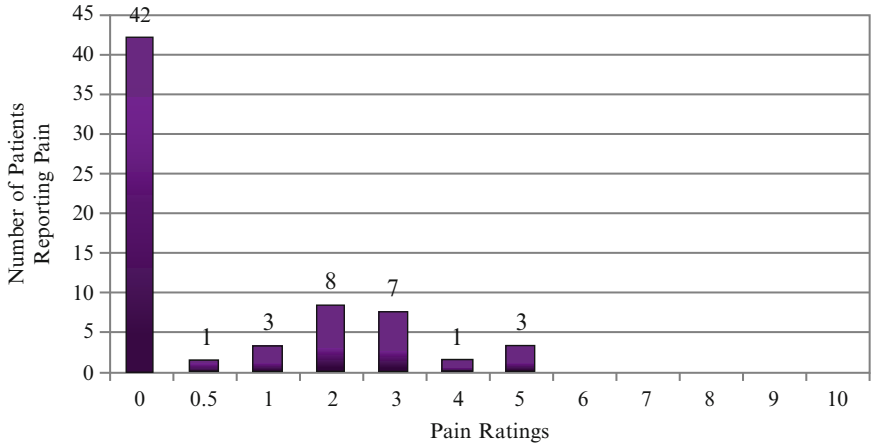

Fig. 14.8 Medication induced pain in ICI (Used with permission of Albaugh, J. and C.E. Ferrans, Patient-reported pain with initial intracavernosal injection. J Sex Med, 2009; 6(2): 513–9)

Contraindications to ICI and Side Effects Summary Points

- Contraindications to ICI: sickle-cell disease, multiple myeloma, and leukemia, Peyronie's, cavernosal fibrosis, and patients in whom sexual activity is not advisable.
- Anticoagulation is not a contraindication to intracavernosal injections.
- Patients on ICI need to be educated about priapism. A prescription for two tablets of terbutaline 5 mg or instructions on pseudoephedrine use may be helpful in inducing detumescence, thus reducing ER visits for prolonged erections and priapism.
- Fibrosis is a serious side effect tied to papaverine use that warrants at least temporary discontinuation of treatment.
- Pain is reported as a side effect in many studies. However, it is insignificant in a large majority of cases and should not deter trial of ICI.

Muse®

Efficacy

MUSE® (Medicated Urethral System for Erection, Meda Pharmaceuticals) is an alternative way to deliver alprostadil to the corporal bodies. MUSE® involves the insertion of the delivery catheter into the meatus and depositing an alprostadil pellet in the urethra. One of the largest studies to describe the efficacy of MUSE® was published by Padma-Nathan et al. [40]. Notable in this study, 995/1511 patients had in-office responses to MUSE®. Of those patients with in-clinic response to MUSE®, only 299 of the 461 patients assigned to the MUSE® arm of the trial achieved intercourse at home. Thus, the true success rate of MUSE® in this large study was only 42–44 %. Furthermore, of the patients who did achieve intercourse at home, only 73 % of doses (2634/3593) were successful in achieving intercourse, orgasm, or a 10 min erection sufficient for intercourse. MUSE® is also efficacious in men who have undergone radical prostatectomy. Costabile et al. [41] reported a 40 % rate of at home success for MUSE® in a group of 384 men greater than 3 months post-prostatectomy.

There are many direct comparison trials between MUSE® alprostadil and ICI alprostadil, and these are summarized in Table 14.6 (16, 42-44). It is both intuitive and noteworthy that despite the higher success rate of ICI, some studies [42] show that some patients prefer MUSE®. Additionally, it has been suggested as a possible rescue medication after ICI failure [43].

Table 14.6 Success rates of MUSE® (Meda Pharmaceuticals, Somerset, NJ) vs. ICI (success rates listed as rigid erections/all erections sufficient for intercourse)

Trial	# pts	MUSE® success rate (%)	ICI success rate (%)
Porst [42]	103	10/43	48/70
Werthman and Rajfer [44]	100	7/37	49/89
Shabsigh et al. [16]	68	NA/62 (with penile ring)	NA/93

Administration

MUSE® is available in doses of 100, 250, 500 and 1000 μg. The applicator is shown in Fig. 14.9 [45].

Instructions for application include urinating before use. Residual urine in the urethra aids in dissolution and dispersal of the medicine along the urethra. The penis is then pulled straight and held pointing up. The 3.5 cm applicator stem is placed approximately 3 cm into the urethra and the button is depressed. The applicator is moved slightly to separate the pellet from the applicator tip and the applicator is removed. The penis is kept upright and rolled between the hands to aid in dissolution and dispersal of medication. The patient is then advised to walk or stand and not to lay flat for approximately 10 min to aid in blood flow.

Side Effects

MUSE® alprostadil had similar rates of pain to ICI alprostadil, but priapism and fibrosis were rare. Side effect rates are noted in Table 14.7 [16, 40, 42, 44, 46]. Other side effects unique to MUSE® compared to ICI were dizziness, hypotension, and sweating. These occurred at a frequency of 1–6 %. Syncope occurred at a rate of <1 % and urethral bleeding also occurred at a rate of 1–5 %.

One strategy for optimizing erectile function in PDE5 inhibitor failures while still avoiding ICI is to combine MUSE® with PDE5 inhibitors. The theoretical basis of this is strong as sildenafil acts to improve and sustain erections, but does not help in initiation, whereas alprostadil jump-starts erection initiation in addition to aiding in maintenance of erections. Raina et al. [47] published a small study of 23 post-prostatectomy patients unsatisfied with sildenafil. Patient satisfaction was measured using a questionnaire. An improvement from 38 % satisfaction with sildenafil alone to 76 % satisfaction with combined MUSE®/sildenafil was demonstrated.

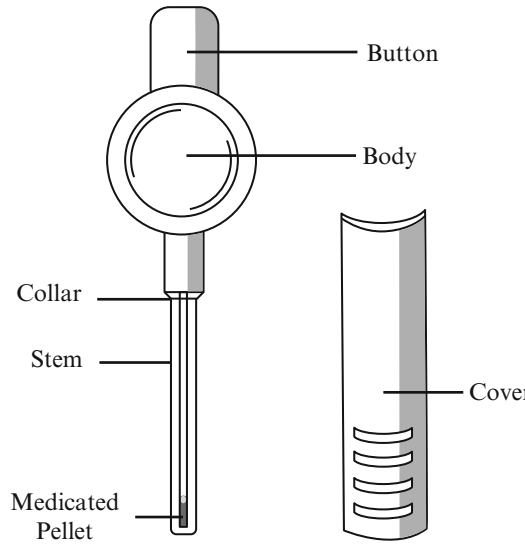

Fig. 14.9 MUSE® applicator (From MUSE® Package Insert. Copyright © Meda Pharmaceuticals, Inc., Somerset, NJ. Used with permission)

MUSE® Summary Points

- MUSE® is less effective than ICI alprostadil (~40 % vs. ~70 %), but patients may prefer the intraurethral route as compared to the injection route.
- Rates of pain, priapism, and fibrosis with MUSE® are comparable to those of ICI alprostadil. Penile hematoma does not occur with MUSE®, but urethral bleeding does occur in ~5 %.

Emerging Trends in ICI

Vasoactive intestinal polypeptide (VIP) is an amino acid neurotransmitter found in the male genital tract that functions to aid in nervous control of smooth muscle activity and penile erection

Table 14.7 Side effects of MUSE® (Meda Pharmaceuticals, Somerset, NJ)

Trial	# pts	Pain (%)	Priapism (%)	Fibrosis (%)
Hellstrom [46]	68	9–18	–	–
Porst [42]	103	31	–	–
Werthman and Rajfer [44]	100	24	1	–
Shabsigh et al. [16]	68	25	–	–
Padma-Nathan et al. [40]	486	33	0	0

[48]. It is thought to relax smooth muscle through activation of cAMP, which in turn causes the veno-occlusion necessary in forming and maintaining an erection [49]. Additionally, it may function along with nitric oxide in controlling erections [49]. VIP-depleted neurons have been found in men afflicted with ED, thus making it a potential target of ED therapy [48]. VIP injection alone has produced tumescence, but promising results have only been shown when used together with the arterial vasodilator phentolamine (VIP/phentolamine). This combination is marketed in Denmark and New Zealand under the name Invicorp® [48, 49]. The initial dose for Invicorp® is VIP 25 μg and phentolamine 1 mg, which can be increased to VIP 25 μg and phentolamine 2 mg if adequate results are not initially reached [48]. VIP/phentolamine is unique in that it typically requires visual or tactile stimulation in order to achieve full rigidity, which more closely mimics the natural coital cycle [48]. Furthermore, the action of VIP/phentolamine subsides after ejaculation while also allowing men to obtain a new erection following additional sexual stimulation [48]. Two independent studies examining psychogenic erectile dysfunction described an 84 % success rate in men obtaining a grade 3 erection (appropriate for intercourse) after treatment with VIP/phentolamine, which is similar to results obtained using other intracavernosal compounds [48]. It also appears to be a viable option when other ICI treatments have failed, with one studying showing a 67 % response rate and another showing a 73 % response rate [49, 50]. The side-effect profile of VIP/phentolamine is favorable compared to other ICIs, with facial flushing being the predominant complaint. Tachycardia/palpitations, headache and dizziness have also been reported in less than 2.2 % of injections [48]. Bruising and bleeding at the injection site along with urethral bleeding have been reported at incidences of less than 8 % [48]. While pain is a common complaint after ICIs, one study involving 236 men reported no pain and another reported significantly lower levels of pain in VIP/phentolamine when compared to alprostadil [51, 52]. Studies looking at priapism and fibrosis, common issues noted with ICI use, show rates of 0.06 and 0 % respectively [48, 51].

Intracavernosal Injection Clinic Visit

Intracavernous injections should not be prescribed without first undergoing instruction and dose titration in the clinic. It may take several visits to find the correct drug and titrate the dose. It is also necessary to obtain consent before starting injections, especially considering the non-FDA approved nature of many of the ICI regimens. The patient should also be thoroughly educated about priapism and instructed on the way to respond to a prolonged erection. It is recommended all patient education be documented and included in the consent process. Namely, the patient should first attempt ejaculation and if this is unsuccessful, oral terbutaline or pseudoephedrine can be taken in an attempt to initiate detumescence. If a painful, non-bendable erection persists after these have been tried, then a visit to the ER is warranted within 2–4 h.

Compounding Pharmacy for ICI Medications

Compounding pharmacies refer to any physical pharmacy that is licensed to mix or compound chemical ingredients for an individual patient that is not otherwise commercially available, based on a prescription ordered by a physician or advanced practice provider. These have typically been smaller local pharmacies [53]. Compounded

medications are similar to the so-called "off-label" use of FDA-approved drugs.

The FDA statement requiring "off-label" medication reminds providers that good medical practice require the physician to use legally available drugs to their best knowledge and judgment. If a provider uses a product for an indication not in the approved labeling, it is the provider's responsibility to be well informed about the product, have good scientific rational and sound medical evidence, and maintain records of the product's use and effects. See http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm.

Compounding is a well-regulated practice. State boards of pharmacy, state medical boards, the Food and Drug Administration (FDA), the Federal Trade Commission (FTC), the Drug Enforcement Agency (DEA), and other federal and state agencies all have some degree of oversight regarding pharmacy compounding practice. The United States Pharmacopeia (UPS), established in the 1820s, is the official governing body setting national standards for compounding pharmacies. Additionally, the Pharmacy Compounding Accreditation Board has a critical role in compounding regulations. Together, they have constructed a web of regulations and standards that protect patients.

Despite these efforts, in the fall of 2012 in Massachusetts, the New England Compounding Center, a commercial compounding pharmacy, was at the center of a deadly meningitis outbreak whose contaminated steroid shots were linked to 45 deaths and 651 illnesses drawing national attention to compounding pharmacies [54]. The Pew Charitable Trusts has identified over 25 pharmacy compounding errors associated with 1049 adverse events, including 89 deaths, since 2001, none of these errors or deaths has been linked to penile injections [55]. The use of compounded drugs for individual patient use is low, only one to three percent of prescriptions filled in the USA by community pharmacies are estimated to be for compounded medications. The percentage of compounds used in hospitals, especially those for intravenous therapy, is significantly greater [53].

Pharmacies like the one in Massachusetts that function like manufacturers mixing large batches of medications without specific prescriptions for patients are now subject to new legislation.

The US Congress passed the Drug Quality and Security Act (DQSA), and signed into law by President Obama in November 2013. The act established a new regulatory category "outsourcing facilities" or 503B for large scale-compounding pharmacies. The facilities are subject to more rigorous quality and safety standards which are modeled after the current Good Manufacturing Practices (CGMPs) that apply to pharmaceutical manufacturers and enforced by the (FDA) [54]. The law reinstated Section 503A as a safe harbor for traditional smaller compounding practices and exempts the traditional compounders from complying with CGMPs. However, it does require compliance with general chapters on compounding, specifically chapters UPS 795 for compounding non-sterile drugs, UPS 797 for compounding sterile dugs and UPS 800 for preparation of hazardous drugs set forth by the US Pharmacopeia Convention (UPS) and are subject to state supervision [56, 57]. The FDA is now involved in regulating compounding under 503A, and is responsible for ensuring the purity and quality of ingredients used in compounding. Furthermore, compounded medications should be prepared using ingredients that come from FDA-registered facilities, the same ones that supply drug manufacturers. The FDA also has the authority to inspect any pharmacies facilities, equipment, and ingredients [56].

The International Academy of Compounding Pharmacists (IACP) has issued guidelines for the labeling of compounded medications. These are designed to help pharmacists communicate to their patients that their prescribed medication is compounded in a pharmacy, how to use and care for the medication, and that their doctor or pharmacist can provide additional information. The IACP guidelines are meant to encourage pharmacists to go beyond what the laws require to ensure patients understand the unique value of compounded mediations. These guidelines provide a standardized labeling model for compounded medicines across all 50 states [53].

The IACP developed a Compounding Pharmacy Assessment Questionnaire (CPAQ™) to facilitate discussions and the establishment of collaborative and referral relationships between prescribers, clinics, hospitals, other pharmacies, and its members. IACP provides a free Pharmacy Locator Service to assist consumers and health professionals in identifying local compounders. Visit IACP's Website at www.iacprx.org or call (800) 927–4227.

The ultimate result of this new legislation forbids providers from storing and utilizing any compounded material in a multidose vial. Products that meet the higher quality control standards such as injectable testosterone from an FDA approved manufacturer can be given to multiple patients. However, stored compounded medications for ICI, since not subject to the same quality standards, are only allowed to be given for single patient use. This limits potential negative consequence (infection, etc.) to a single patient as opposed to what happened in the aforementioned NE compounding center. Single patient medications also facilitate epidemiological tracking and identification of potentially dangerous or contaminated products.

Intracavernous Injections Summary Points

- Intracavernous injections should not be prescribed without first undergoing instruction and dose titration in the clinic.
- Obtain consent before starting injections, especially considering the non-FDA approved nature of many of the ICI regimens.
- The patient should also be thoroughly educated about priapism and instructed on the way to respond to a prolonged erection.
- Compounding is a well-regulated practice.
- Medications are similar to "off-label" use of FDA approved drugs.
- 503a Pharmacies compounding medications for individual patient use with a prescription are exempt from the Good Manufacturing Practices (CGMPs) under the new Drug Quality and Security Act (DQSA). However, they do have to comply with the general chapters <795> compounding non-sterile pharmaceuticals, <797> compounding sterile pharmaceuticals and <800> preparation of hazardous drug by the UPS conference.
- 503b Outsourcing facilities for large scale compounding pharmacies must now follow the CGMPs that apply to pharmaceutical manufacturers and are enforced by the FDA.
- Utilize the IACP Compounding Pharmacy Assessment Questionnaire (CPAQ™).
- Know state laws and regulations regarding state specific requirements (for example dose your state require out of state 503b compounding pharmacies to be registered in your home state).
- Visit the compounding pharmacy.
- Pharmacy should be following the UPS standards for compounding and labeling.

Topical Agents

Efficacy

Compared with both oral and injection therapies, topical routes are quite attractive. Theoretically, systemic effects are minimized compared to the oral route, and it is certainly less invasive, and thus would undoubtedly be more popular than injection or intraurethral therapies. To date, however, no sufficiently effective product exists. Topical alprostadil was combined with agents to improve skin penetration (SEPA and NexACT). Vitaros, the combination of alprostadil and NexACT, formerly called Alprox-TD, has been recently denied approval by the FDA due to potential carcinogenicity [58]. In trials of alprostadil with SEPA, doses of 2500 μg alprostadil were used with a resulting 39 % of patients achieving erection sufficient for penetration vs. 7 % of the placebo group [59]. Unfortunately, baseline characteristics were not provided in this study. Ultimately, alprostadil/SEPA trials were discontinued because of their apparent lack of efficacy at safe doses.

A large trial of topical alprostadil without a skin penetration enhancer was also published by

Padma-Nathan and Yeager [60] which showed a statistically significant, but very slight improvement in sexual function with topical alprostadil. This study used 100, 200, and 300 μg doses of alprostadil and achieved successful penetration rates of 57.5 %, up from a baseline of 50 % at the highest dose. A criticism of this study is that its high initial function rates do not adequately represent population seeking treatment for erectile dysfunction.

Topical minoxidil, nitroglycerin, and papaverine were also tested variably alone and with skin penetration enhancers, but with little success.

Topical Agent Summary

No agents are currently FDA approved for topical use, and none are currently being widely used off label.

Treatment of Erectile Dysfunction After Radical Prostatectomy

Treatment of erectile dysfunction in post-prostatectomy men is unique compared with ED caused by other factors in that rehabilitation (ED recovery) from treatment induced nerve and vascular injury are plausible. Thus, treatment of post-prostatectomy ED must keep two goals in mind: immediate erectile function facilitated by medication use and ultimate return to pre-prostatectomy erection status without use of adjunctive medications. Recovery of erectile function after RP can take up to 48 months [61]. Higher preoperative sexual health-related quality of life scores, lower body mass index, younger age, and lower serum PSA scores have all been shown to be associated with better functional erections at 2 years after RP [62].

Several studies suggest the potential of pharmacotherapy to aid in a rehabilitation process to return baseline erectile function status with the goal of optimizing function of spontaneous erections. In rats it has been found that denervating the cavernosum causes hypoxia, fibrosis [63, 64] and cell apoptosis [65], Further, PDE5I's have been shown to assist in neurogenesis in rats after an induced stroke [66]. This combined with the knowledge that erections increase the oxygenation of the cavernosum argue towards potential for return to baseline erectile function with rehabilitation.

The concept of penile rehabilitation after RP was first introduced in the 1990s when Montorsi et al. [67] published one of the first papers on erectile rehabilitation comparing 3 months of ICI alprostadil injected three times per week (t.i.w.) to patients receiving no treatment. Patients were assessed at a 6-month follow-up. Eight of twelve (67 %) ICI patients were noted to have return of spontaneous erection. The other four patients (33 %) in the ICI group reported needing to use ICI greater than 50 % of the time to achieve successful intercourse. Only 20 % of the placebo group reported spontaneous erections that were sufficient for intercourse. To date no other study has been able to replicate this impressive result, which raises concerns regarding methodological flaws including low number of patients.

Penile injections do not require neuronal integrity to function. Injections have been shown to have the highest functional erection success rates following RP with multiple studies showing ≥90 % efficacy at 6 months after RP [68, 69]. A larger study by Mulhall et al. [70] examined a group of men with functional preoperative erections prior to prostatectomy and who were nonresponders to sildenafil in the early post-operative period. At 18 months after surgery, men who followed a regimen of t.i.w. ICI were compared to those who did not follow the protocol. Of the 58 men in the protocol group, 52 % had a return of spontaneous erections compared to 19 % of the 74 men in the non-protocol group. Although these results are encouraging, the study suffers from a high degree of self-selection bias, as the patients who were not having success and ultimately stopped treatment, but adhered to follow-up were simply included in the non-protocol group.

Like penile injections, MUSE® works independent of nerve status. This medication has been shown to be effective in men with ED after RP, producing an erection thought to be sufficient

for intercourse in the clinic in 70 % of subjects, and leading to successful intercourse at home in 40 % of subjects compared to 7 % in placebo [41]. Similar results were found in a study where 55 % of subjects had successful intercourse and 48 % effectively used MUSE® long term (2 years) after RP [71]. Raina et al. [72] reported 97 post-prostatectomy men, 56 of whom used t.i.w. MUSE™ for 6 months and 35 of whom used only p.r.n. erectile aids. Those who used MUSE® attained a fourfold higher rate of spontaneous erections than those who did not (40 % vs. 11 %). In 2010, McCullough et al. [73] compared the effectiveness of MUSE® to sildenafil in a large randomized prospective study. They showed no significant differences in IIEF erectile function scores and intercourse success rates. However, at 6 months the MUSE® group had significantly better global assessment question scores compared to sildenafil.

Oral phosphodiesterase 5 inhibitors (PDE5I's) are the most commonly used rehabilitative pharmaceutical though they are thought to have lower rehabilitative potential than ICI or MUSE® as they require a threshold level of neural integrity to be effective. Rates of return to spontaneous erection with ICI and MUSE® should theoretically be higher because they are more effective at producing erections during the neurapraxic period post prostatectomy.

There have been a number of large multicenter randomized double-blind controlled studies evaluating PDE5I's in penile rehabilitation immediately after RP. Padma-Nathan et al. [74] were the first to show benefit from PDE5I vs. placebo. Specifically, men receiving nightly sildenafil (50 or 100 mg) had an increased return of spontaneous erectile function than those taking placebo: 24 % for 50 mg sildenafil and 33 % for 100 mg sildenafil vs. 5 % for placebo. Also, the IIEF-EF scores were higher in the sildenafil groups compared to placebo (13.1 vs. 8.8). Montorsi et al. [75] compared daily vardenafil to on-demand vardenafil, and a placebo. They found no difference in erectile recovery between on-demand and nightly dosing with vardenafil after RP. However, the groups receiving nightly or on-demand vardenafil had significantly greater IIEF scores than placebo throughout the 9 month trial period. The benefit seen in the on-demand group was lost during the 2-month drug free washout period. Interestingly vardenafil on-demand was superior to vardenafil nightly when comparing SEP-3 success rates (45.9 % vs. 34.5 %).

Montorsi et al. [76] in 2014 demonstrated that although nightly tadalafil vs. placebo was associated with a higher percentage of men with IIEF-EF >21 after 9 months (25.2 % vs. 14.2 %) the benefit was lost after a drug free washout. Notably, there was less penile shrinkage in the tadalafil nightly group vs. placebo at 9 months (2.2 mm vs. 6.3 mm). See Chap. 20 for a detailed description on penile rehabilitation and the specific role of PDE5I.

Post-prostatectomy Penile Rehabilitation Summary Points

- Efficacy in achieving erections adequate for penetration in the post prostatectomy setting is well established for ICI (≥90 %) and MUSE® (40–55 %).
- Intracavernous injections and MUSE® have both been studied for rehabilitation potential in post-prostatectomy patients. In small studies, 40–60 % of patients who were potent prior to prostatectomy regained unassisted erectile function; this is compared to only 10–20 % who did not use MUSE® or ICI (Table 14.8).
- Oral PDE5Is are most commonly used for penile rehabilitation and there is growing evidence that they can improve post-prostatectomy erections. However, long-term data are unknown (Table 14.9).

Conclusion

Intracavernosal injection therapy and MUSE™ remain excellent treatment options for men suffering from erectile dysfunction. Both have demonstrated effectiveness in numerous settings, and are especially relevant in men for whom PDE5I therapy is contraindicated, not tolerated, or inef-

Table 14.8 Chapter summary table

Drug	Mechanism	Efficacy	Side effects	Comments
ICI alprostadil	Increases cAMP and cGMP	>70 %	Pain ~7 %	High efficacy, good first line for ICI, reputation as causing highest rates of pain not borne out in head to head trials
			Priapism <1 %	
			Fibrosis <1 %	
ICI papaverine	Nonspecific PDE inhibitor	39–61 %	Pain 4 %	Rarely used as solo therapy, efficacy and fibrosis both dose dependent
			Priapism 7 %	
			Fibrosis 6 %	
ICI phentolamine	Alpha-blocker	NA	NA	Rarely used as solo therapy
Bimix (papaverine + phentolamine)	PDE inhibitor + alpha-blocker	68.5 %	Pain 12 %	High efficacy, poor side effect profile
			Priapism 8 %	
			Fibrosis 12 %	
Trimix (papaverine + phentolamine + alprostadil)	Direct and indirect increase in cAMP/cGMP + PDE inhibitor + alpha-blocker	>70 %, up to 90 %	Pain 12–15 %	High efficacy, low side effects, low cost
			Priapism 5 %	
			Fibrosis 4 %	
			Variable, dependent on mixture/dose	
Quadmix (papaverine + phentolamine + alprostadil + atropine)	Release of endothelium derived relaxing factor (Direct and indirect increase in cAMP/cGMP + PDE inhibitor + alpha-blocker)	As per trimix	Similar to trimix	No apparent additional efficacy over trimix
MUSE®	Increases cAMP and cGMP	~40 %	Pain ~25–30 %	Intermediate range efficacy, usually more acceptable to patients than ICI
			Urethral bleeding 5 %	
Topicals (main investigational drug was alprostadil)	Dependent on drug	Very poor in safe doses	Genital "warmth" to severe genital pain, dose dependent	None are currently on the market, no accepted off-label use

Table 14.9 Penile rehabilitation: rates of return of spontaneous erectile function with different pharmacotherapy regimens

Therapy/study	Study size	Time of assessment (months post RP)	Treatment group	Non-treatment group
PDE5I				
Padma-Nathan et al. [74]	123 (40 pts @ 50 mg sildenafil, 41 @ 100 mg, 42 placebo)	9	26 %, 29 %	4 %
Montorsi et al. [75]	628 (210 pts @ 10 mg vardenafil nightly, 208 @ 5–20 mg on demand, 210 placebo)	9+2 Month drug free washout	32 %,48 %	25 %
Montorsi et al. [76]	422 (139 pts @ 5 mg tadalafil daily, 142 @ 20 mg on demand, 141 placebo)	9	25 %, 19 %	14 %
ICI				
Montorsi et al. [67]	27 (12 ICI, 15 no tx)	6	67 %	20 %
Mulhall et al. [70]	132 (58 ICI protocol, 74 non protocol)	18	52 %	19 %
MUSE®				
Raina et al. [72]	91 (56 MUSE®, 35 prn)	9	40 %	11 %

fective. ICI and MUSE® maintain effectiveness in the post-prostatectomy period, and likely will play a central role in aggressive penile rehabilitation programs.

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References

1. Wysowski DK, Swann J. Use of medications for erectile dysfunction in the United States, 1996 through 2001. J Urol. 2003;169(3):1040–2.
2. McMahon CG, Samali R, Johnson H. Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. J Urol. 2000;164(4):1192–6.
3. Hatzichristou DG, et al. Sildenafil versus intracavernous injection therapy: efficacy and preference in patients on intracavernous injection for more than 1 year. J Urol. 2000;164(4):1197–200.
4. Palmer LS, et al. Characterization of cyclic AMP accumulation in cultured human corpus cavernosum smooth muscle cells. J Urol. 1994;152(4):1308–14.
5. Molderings GJ, van Ahlen H, Gothert M. Modulation of noradrenaline release in human corpus cavernosum by presynaptic prostaglandin receptors. Int J Impot Res. 1992;4:19–25.
6. Kifor I, et al. Tissue angiotensin II as a modulator of erectile function. I. Angiotensin peptide content, secretion and effects in the corpus cavernosum. J Urol. 1997;157(5):1920–5.
7. Porst H. The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. J Urol. 1996;155(3):802–15.
8. Porst H, et al. Intracavernous alprostadil alfadex—an effective and well tolerated treatment for erectile dysfunction. Results of a long-term European study. Int J Impot Res. 1998;10(4):225–31.
9. Shabsigh R, et al. Intracavernous alprostadil alfadex (EDEX/VIRIDAL) is effective and safe in patients with erectile dysfunction after failing sildenafil (Viagra). Urology. 2000;55(4):477–80.
10. Nagai A, et al. Intracavernous injection of prostaglandin E1 is effective in patients with erectile dysfunction not responding to phosphodiseterase 5 inhibitors. Acta Med Okayama. 2005;59(6):279–80.
11. 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(6):1992–7. discussion 1997–8.
12. Caverject® Package Insert. Pfizer Inc.
13. Caverject® Impulse Package Insert. Pfizer Inc.
14. Edex® Package Insert. Endo/Auxilium Pharmaceuticals Inc.
15. Group EAS. The long-term safety of alprostadil (prostaglandin-E1) in patients with erectile dysfunction. The European Alprostadil Study Group. Br J Urol. 1998;82(4):538–43.
16. Shabsigh R, et al. Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicenter study. Urology. 2000;55(1):109–13.

17. Lue TF, Broderick GA. Evaluation and nonsurgical management of erectile dysfunction and premature ejaculation. In: Wein LRKJ, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 9th ed. Philadelphia, PA: Saunders; 2007.
18. Virag R. Intracavernous injection of papaverine for erectile failure. Lancet. 1982;2(8304):938.
19. Virag R, Daniel C, Sussmann H, Bouilly P, Virag H. Self intracavernous injection of vasoactive drugs for the treatment of psychogenic and neurologic impotence (late results in 109 patients). In: Proceedings, 5th conference on vasculogenic impotence and corpus cavernosum revascularization; 2nd world meeting on impotence, Prague. Accessed 13 Oct 1986.
20. Beretta G, et al. Intracavernous injection of papaverine in paraplegic males. Acta Eur Fertil. 1986;17(4): 283–4.
21. Brindley GS. Maintenance treatment of erectile impotence by cavernosal unstriated muscle relaxant injection. Br J Psychiatry. 1986;149:210–5.
22. Kirkeby HJ, Johannesen NL. Pharmacologically induced prolonged erections produced by papaverine. Follow-up of injection therapy. Scand J Urol Nephrol Suppl. 1989;125:97–100.
23. Kirkeby HJ, Petersen T, Poulsen EU. Pharmacologically induced erection in patients with multiple sclerosis. Scand J Urol Nephrol. 1988;22(4):241–4.
24. Virag R, Nollet F, Greco E, Floresco J. Long term evaluation of local complications of self intracavernous injections (SICI). Int J Impot Res. 1994;6:A37.
25. Driemen PM. Papaverine--hepatotoxic or not? J Am Geriatr Soc. 1973;21(5):202–5.
26. Blum MD, et al. Effect of local alpha-adrenergic blockade on human penile erection. J Urol. 1985;134(3):479–81.
27. Derouet H, Meeth M, Bewermeier H. Experience with a papaverine/phentolamine/prostaglandin E1-mixture in non-responders to autoinjection therapy. Aktuelle Urol. 1996;27:217–74.
28. Albaugh JA. Intracavernosal injection algorithm. Urol Nurs. 2006;26(6):449–53.
29. Bechara A, et al. Prostaglandin E1 versus mixture of prostaglandin E1, papaverine and phentolamine in nonresponders to high papaverine plus phentolamine doses. J Urol. 1996;155(3):913–4.
30. Seyam R, et al. A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E1. Int J Impot Res. 2005;17(4):346–53.
31. Moemen MN, et al. Clinical and sonographic assessment of the side effects of intracavernous injection of vasoactive substances. Int J Impot Res. 2004;16(2): 143–5.
32. Kulaksizoglu H, Hakim LS, Nehra A, Goldstein I. Comparison of alprostadil sterile powder (Caverject™) with trimix nomogram and patient satisfaction. Abstract #699. J Urol. 1997;157:180.
33. Sogari PR, Teloken C, Souto CA. Atropine role in the pharmacological erection test: study of 228 patients. J Urol. 1997;158(5):1760–3.
34. Pharmacy Creations R. New Jersey, erectile dysfunction compounds price list. Accessed 16 Sept 2008.
35. Limoge JP, et al. Minimally invasive therapies in the treatment of erectile dysfunction in anticoagulated cases: a study of satisfaction and safety. J Urol. 1996;155(4):1276–9.
36. Lowe FC, Jarow JP. Placebo-controlled study of oral terbutaline and pseudoephedrine in management of prostaglandin E1-induced prolonged erections. Urology. 1993;42(1):51–3. discussion 53–4.
37. Priyadarshi S. Oral terbutaline in the management of pharmacologically induced prolonged erection. Int J Impot Res. 2004;16(5):424–6.
38. Tsao AK, Nehra A. Intracavernosal injection of vasoactive agents. In: Mulcahy JJ, editor. Current clinical urology: male sexual function: a guide to clinical management. 2nd ed. Totowa, NJ: Humana Press Inc; 2006.
39. Albaugh J, Ferrans CE. Patient-reported pain with initial intracavernosal injection. J Sex Med. 2009; 6(2):513–9.
40. Padma-Nathan H, et al. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. N Engl J Med. 1997;336(1):1–7.
41. Costabile RA, et al. Efficacy and safety of transurethral alprostadil in patients with erectile dysfunction following radical prostatectomy. J Urol. 1998;160(4): 1325–8.
42. Porst H. Transurethral alprostadil with MUSE (medicated urethral system for erection) vs intracavernous alprostadil—a comparative study in 103 patients with erectile dysfunction. Int J Impot Res. 1997;9(4):187–92.
43. Engel JD, McVary KT. Transurethral alprostadil as therapy for patients who withdrew from or failed prior intracavernous injection therapy. Urology. 1998;51(5): 687–92.
44. Werthman P, Rajfer J. MUSE therapy: preliminary clinical observations. Urology. 1997;50(5):809–11.
45. MUSE® Package Insert. Meda Pharmaceuticals Inc.
46. Hellstrom WJ, et al. A double-blind, placebo-controlled evaluation of the erectile response to transurethral alprostadil. Urology. 1996;48(6):851–6.
47. Raina R, et al. Combination therapy: medicated urethral system for erection enhances sexual satisfaction in sildenafil citrate failure following nerve-sparing radical prostatectomy. J Androl. 2005;26(6):757–60.
48. Dinsmore WW, Wyllie MJ. Vasoactive intestinal polypeptide/phentolamine for intracavernosal injection in erectile dysfunction. BJU Int. 2008;102(8): 933–7.
49. Sandhu D, et al. A double blind, placebo controlled study of intracavernosal vasoactive intestinal polypeptide and phenotolamine mesylate in a novel auto-injector for the treatment of non-psychogenic erectile dysfunction. Int J Impot Res. 1999;11(2):91–7.

50. Dinsmore WW, Alderdice DK. Vasoactive intestinal polypeptide and phentolamine mesylate administered by autoinjector in the treatment of patients with erectile dysfunction resistant to other intracavernosal agents. Br J Urol. 1998;81(3):437–40.
51. Dinsmore WW, et al. Treating men with predominantly nonpsychogenic erectile dysfunction with intracavernosal vasoactive intestinal polypeptide and phentolamine mesylate in a novel auto-injector system: a multicentre double-blind placebo-controlled study. BJU Int. 1999;83(3):274–9.
52. Shah PJ, et al. Injection therapy for the treatment of erectile dysfunction: a comparison between alprostadil and a combination of vasoactive intestinal polypeptide and phentolamine mesilate. Curr Med Res Opin. 2007;23(10):2577–83.
53. Pharmacists IIAoC. Backgrounder on compounding pharmacy: fact sheet. 2015.
54. Clinical IQ, LacbtPCT. Quality standards for large scale sterile compounding facilities. 2014. Accessed 30 Mar 2015.
55. Trust PC. U.S. Illnesses and deaths associated with compounded medications. http://www.pewtrusts.org. Accessed 14 Sept 2014.
56. FDA. Guidance: pharmacy compounding of human drug products under section 503A of the Federal Food, Drug, and Cosmetic Act. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf. Accessed 30 Mar 2015.
57. Convention U.S.P. UPS chapters. http://www.usp.org/about-usp. Accessed 30 Mar 2015.
58. Vitaros N. 2008. http://www.nexmed.com/products/TopicalED.php. Accessed 28 Nov 2008.
59. 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(2):301–5.
60. Padma-Nathan H, Yeager JL. An integrated analysis of alprostadil topical cream for the treatment of erectile dysfunction in 1732 patients. Urology. 2006;68(2):386–91.
61. Mulhall JP. Defining and reporting erectile function outcomes after radical prostatectomy: challenges and misconceptions. J Urol. 2009;181(2):462–71.
62. Alemozaffar M, et al. Prediction of erectile function following treatment for prostate cancer. JAMA. 2011;306(11):1205–14.
63. Leungwattanakij S, et al. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. J Androl. 2003;24(2):239–45.
64. Hu WL, et al. Fibrosis of corpus cavernosum in animals following cavernous nerve ablation. Asian J Androl. 2004;6(2):111–6.
65. User HM, et al. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol. 2003;169(3):1175–9.
66. Zhang R, et al. Sildenafil (Viagra) induces neurogenesis and promotes functional recovery after stroke in rats. Stroke. 2002;33(11):2675–80.
67. Montorsi F, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol. 1997;158(4):1408–10.
68. Calahorra Fernandez FJ, et al. Penile self-injection of a papaverine-phentolamine combination, as treatment of impotence, in patients treated with radical cystoprostatectomy. Actas Urol Esp. 1991;15(1):43–5.
69. Claro Jde A, et al. Intracavernous injection in the treatment of erectile dysfunction after radical prostatectomy: an observational study. Sao Paulo Med J. 2001;119(4):135–7.
70. Mulhall J, et al. The use of an erectogenic pharmacotherapy regimen following radical prostatectomy improves recovery of spontaneous erectile function. J Sex Med. 2005;2(4):532–40. discussion 540–2.
71. Raina R, et al. Long-term efficacy and compliance of MUSE for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. Int J Impot Res. 2005;17(1):86–90.
72. Raina R, et al. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. BJU Int. 2007;100(6):1317–21.
73. McCullough AR, et al. Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus sildenafil citrate. J Urol. 2010;183(6):2451–6.
74. Padma-Nathan H, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res. 2008;20(5):479–86.
75. Montorsi F, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54(4):924–31.
76. Montorsi F, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol. 2014;65(3):587–96.

Penile Prosthesis

15

Kenneth J. DeLay Jr. and Tobias S. Köhler

Introduction

Treatment of erectile dysfunction with implantation of a penile prosthesis has the highest satisfaction rates for patient with severe erectile dysfunction with rates between 69 and 98 % [1–11]. Studies suggest that for patients who have tried all therapies that penile prosthesis has greater patient satisfaction that PDE5I or ICI. The penile prosthesis was introduced to the market over 40 years ago by F. Brantley Scott, Professor of Urology at Baylor. Types of penile prostheses include: semi-rigid and inflatable. Continued innovations with implants has brought about increased device longevity, technically easier implantation, and decreased rates of infection. Thorough counseling of the patient is necessary to patient's satisfaction with the device.

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Models of Penile Prosthesis

There are two main vendors for penile prosthesis: Coloplast (Minneapolis, MN, USA) and American Medical Systems (Boston Scientific, Marlborough, MA, USA). There are three penile prosthesis options: Semirigid, Two-piece inflatable, and three-piece inflatable. A three-piece penile prosthesis consists of cylinders, a reservoir, and a pump in addition to the tubing.

The paired cylinders are implanted in the corpora cavernosa. The pump is implanted into the scrotum. The reservoir can be implanted either into the space of Retzius or ectopically between the transversalis fascia and the remainder of the abdominal wall. The reservoir is filled with normal saline. Compression of the pump transfers fluid into the cylinders from the reservoir resulting in an erection. Compression of the release valve transfers fluid from the cylinders into the reservoir. A lock-out valve prevents auto inflation.

Cylinder

AMS offered three models of inflatable penile prosthesis: AMS 700™ CX, CXR, and LGX. The AMS 700 CX has historically been the gold standard with the base diameter of 10 mm and expands in girth to a fixed 18 mm. The CXR has a cylinder base of 9 mm with the

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Fig. 15.1 AMS 3-piece IPP with LGX cylinders (Used with permission. Copyright © Boston Scientific Corp., Marlborough, MA. All Rights Reserved)

Fig. 15.2 AMS 2-piece Ambicor prosthesis (Used with permission. Copyright © Boston Scientific Corp., Marlborough, MA. All Rights Reserved)

Fig. 15.3 Coloplast 3-piece IPP, the Titan with one-touch release pump (Used with permission. Copyright © Coloplast Corp., Minneapolis, MN. All Rights Reserved)

inflatable portion expanding to 14.5 mm. These properties make the CXR ideal for patient with scarred corporal bodies (prior surgery, history of priapism) and patients with a small penis. The LGX cylinders expand in girth to 18 mm with a length expansion of 15–20 % (Fig. 15.1). The AMS 3-piece implants are coated with Inhibizone™ that helps reduce infection rates. AMS offers the only two piece inflatable penile prosthesis, the Ambicor™, which is ideal in cases where reservoir placement requires an undue risk (history of renal transplant or neobladder) (Fig. 15.2). The Ambicor is not coated in Inhibizone. AMS cylinders are offered in 12, 15, 18, and 21 cm sizes. Rear tips come in ½, 1, 1½ (stackable), 2, 3, 4, 5, and 6 cm sizes and can be stacked for a maximum length of 7½ cm. AMS offers the Spectra malleable which is non-antibiotic coated and comes in girths of 9.5, 11, and 13 mm.

Coloplast manufactures a three piece IPP, the Titan® (Fig. 15.3). It comes with the One-Touch Release pump, which allows for deflation without having to hold the deflate button continuously

Fig. 15.4 Coloplast malleable prosthesis, the genesis (Used with permission. Copyright © Coloplast Corp., Minneapolis, MN. All Rights Reserved)

[12]. The Titan comes with both narrow base and standard cylinder types. The NB base is 10 mm with a 17 mm cylinder bladder upon expansion. The standard cylinders have a 12 mm base and a 21 mm cylinder bladder upon expansion. Coloplast standard cylinders come in 14, 16, 18, 20, 22 pre-connected sizes and 24, 26, and 28 cm non-pre-connected cylinder lengths. The rear tips for standard size include 1, 1½, 2, and 3 cm which are stackable to 7½ cm. The Titan narrow base comes in 11 and 14 cm lengths with similar sized narrow rear tips. The Titan comes with a hydrophilic coating allowing for soaking in an antibiotic solution. Coloplast also manufactures the Genesis malleable (Fig. 15.4). It is hydrophilically coated and is cut to proper length intraoperatively. It comes in different girths of 9.5, 11, and 13 mm.

Reservoir

Modified versions of their reservoir have been introduced by both manufacturers to aid in ectopic reservoir placement. Coloplast has introduced their CL reservoir whose cloverleaf design allows for a larger fluid without being as prominent. AMS introduced the conceal reservoir which can be easily slipped between tissue layers (Fig. 15.5). Both have lock-out valves preventing auto inflation. This is a particularly important feature when the reservoir is placed outside of the space of Retzius.

Fig. 15.5 AMS 3-piece IPP with the conceal reservoir (Used with permission. Copyright © Boston Scientific Corp., Marlborough, MA. All Rights Reserved)

Pump

The pump is to be placed between the internal and external spermatic fascia. Care must be taken to avoid placement that is too superficial which may lead to wound dehiscence and possible infection. The Titan comes with the One-Touch Release pump with AMS presenting the Momentary Squeeze pump, which both allow for detumescense without hold the deflate button continuously. Each carries a diminished risk of auto-inflation compared to their predecessors. Studies with both the One-Touch Release and the Momentary Squeeze pump have demonstrated high rate of patient satisfaction with fewer teaching sessions required [12, 13]. Both devices require aggressive squeezing at the base of the penis to facilitate total device emptying after the release button has been activated.

Preoperative Workup

Given the highly elective nature of insertion of a penile implant appropriate candidate selection and counseling are essential. Men with concomitant post-prostatectomy incontinence should be

counseled regarding the possibility of dual procedure with the simultaneous placement of an artificial urinary sphincter or male sling. Anticoagulation generally should be held prior to surgery, but some series have revealed acceptable outcomes with patients on anticoagulation [14]. Any active infection should be resolved before surgery. Untreated voiding dysfunction secondary to either bladder outlet obstruction or a neurogenic bladder is a contraindication to proceeding with surgical implantation [15].

Penile prostheses provide an on demand erection. Penile sensation and ejaculatory function are preserved with the penile prosthesis. Patient satisfaction is greater with the penile prosthesis than alternative treatments including vacuum erection devices, PDE5I and injections [16]. However, the patient must understand that the device makes latent natural erections as well as utility of less invasive treatment options impossible.

Certain patient factors predispose to dissatisfaction with a penile implant. Realistic expectations, BMI <30, absence of Peyronie's disease, and no history of prostatectomy are positive predictors of satisfaction. Perceived loss of length, decreased glanular engorgement, altered sensation, and partner dissatisfaction predict patient dissatisfaction. The mnemonic CURSED Patient (Compulsive, Unrealistic, Revision, Surgeon Shopping, Entitled, Denial, and Psychiatric) developed by Trost et al. identifies patients particularly prone to dissatisfaction [17].

Potential complications that are listed in the implant package insert include scrotal swelling, pain, new or exacerbation of angulation/curvature, difficulty with ejaculation (typically transient), urinary retention, hematoma with wound leakage, bleeding, delayed wound healing, phimosis, sensory loss, device malfunction, cylinder aneurysm, fibrous capsule formation, over/under-inflation, erosion, inguinal hernia, and/or genital change.

Misconceptions and distorted perception of size contribute to a large bulk of patient dissatisfaction. It is physiologically expected that the implanted penis is not as long as the physiologic erection. Lack of glans engorgement likely contributes to the perception of decreased size. This can be treated with the addition of a PDE5I [18]. The capsule surrounding the device's inability to expand can also contribute to the loss of length. Preoperative and postoperative measurements can help a patient see the length objectively. Ventral scrotoplasty can improve satisfaction by increasing the perceived length. 84 % of patients undergoing a ventral scrotoplasty perceive that they have a longer penis than before surgery [19]. Daily cycling of the device (particularly the LGX) prevents a constricted capsule from forming around the implant. This capsule is thought to be in place by 3 months.

Operative Procedure

Appropriate operative speed and meticulous sterile technique are necessary to minimize the risk of implant infection. Before the availability of coated implants most infections were associated with coagulase negative staphylococcus. Chlorhexidine–alcohol prep reduces skin flora greater than povidone–iodine [20]. Use of the no-touch technique, which prevents implants from touching the skin, has shown an infection rate of 0.46 % [21]. Revision surgery increases the risk of infection [22].

Approaches

While the semi-rigid prostheses can be implanted through a sub-coronal incision, three piece inflatable penile prostheses are placed through either a penoscrotal or an infrapubic approach. Currently the majority of prosthesis implanted in the USA are placed using a penoscrotal approach.

The penoscrotal incision offers excellent exposure of the corporal bodies and makes avoiding the dorsal sensory nerves easier. A Foley catheter is placed at the beginning of the procedure. This simple step has been shown to increase the distance to the bladder during reservoir placement making injury less likely [23]. Simultaneous placement of an artificial urinary sphincter through this approach has been described [24]. The scrotal pump can be directly placed in a dependent position with this approach.

The main disadvantage is that that this approach requires the blind placement of the reservoir into the space of Retzius. This approach also allows for ventral phalloplasty when indicated.

With the penoscrotal approach, after placement of a Foley catheter, an incision is made either vertically or horizontally at the penoscrotal junction. The dartos is divided using electocautery. A ring retractor system is used. The cavernosal bodies are identified and cleared off after identification of the corpus spongiosum. A 1–2 cm corporotomy is made and polyglactin or polydioxanone stay sutures are placed. The spongy tissue is now exposed. Various techniques including serial dilation, single pass with a large dilator or only use of the Furlow measuring device are used to dilate the corpus cavernosa proximally and distally. Care should be taken dilate with the penis distorted laterally to prevent unintended crossover through the fenestrated penile septum and minimize urethral injury. Dilation in the case of fibrotic corporal bodies adds difficulty to the case with risks of perforation rising dramatically. There is an increased risk of both distal urethral and proximal corporal perforation. As discussed later in the chapter, in cases of severe fibrosis cavernotomes may be required.

Next the corporal bodies are measured and the appropriate prosthesis is selected. Minimizing use of rear tip extenders is preferable if possible; however, this must be balanced with the need to avoid a high riding pump within the scrotum. The cylinder to pump length varies with the manufacturer. Care must be taken to properly size the implant and use adequate rear tips to optimize penile length and pump location. AMS recommends subtracting 2 cm from the measured length and selecting cylinder shorter or equal to this length. Coloplast tubing lengths increase as the cylinders get longer. To size a Coloplast cylinder the difference between the proximal measurement and 10 is taken. The difference indicates the length of rear tip extenders required while no rear tip extenders are required if the number is zero or negative.

Perforation of the urethra or tunica albuginea of the corporal bodies can occur during dilation. There is a 4.5 % incidence of proximal perforation with a novel prosthesis with up to 37 % in difficult revisions [25, 26]. Proximal perforations are more common than lateral perforations. Perforation of the tunica albuginea is more likely to occur with smaller dilators. Proximal perforations are readily repaired with a rear tip extender sling where a suture is passed through the rear tip extender and anchored to the corporal bodies [27]. Lateral perforations can easily be closed with a simple suture in the tunica albuginea. Undiagnosed distal/lateral perforations will present as an extrusion.

The distal cylinder is brought into the distal corporal body using the Furlow inserter. Prepacking suture is placed through a needle which is then loaded into the Furlow. The Furlow is then passed through the corporotomy and guided into to the distal corporal body until it is snug against the glans. The needle is then fired through the glans avoiding urethral injury. By pulling the suture the distal tip of the cylinder is brought securely into the glans. The procedure is repeated on the contralateral side. The proximal halves of the cylinders are then seated. The corporal bodies are then closed by tying the stay sutures to one another.

Cylinder crossover can be difficult to recognize although it is believed to occur in up to 25 % of cases [28]. This occurs when there is perforation of the intercavernous septum. This can be prevented by aiming the dilators laterally and dorsally. When crossover occurs portions of both cylinders lie within the same corporal body with an over and back phenomenon. Upon inflation of the prosthesis, the phallus is subtly crooked but later becomes quite obvious. Crossover is easily corrected by placing a large dilator into the receiving side of the crossover and then redilating with subsequent cylinder placement on the contralateral side.

Distal urethral injury is a feared intraoperative complication which can lead to termination of the procedure. With the penoscrotal approach a Foley should be placed for urethral identification and bladder decompression. Urethral injury can occur upon scrotal dissection, distal dilation or during penile modeling. Injury during scrotal dissection can be repaired with a two layered closure and proceeding with implant placement. If a

urethral laceration is repaired during the scrotal dissection a Foley catheter should be left for 3–5 days [29]. Appropriately aiming the dilators dorsolaterally during distal dilation can prevent distal urethral injury. If upon irrigating the corporal bodies, fluid comes out of the urethral meatus the distal urethra has been perforated. If the injury occurs before any components have been implanted then the case should be terminated and redone in 3 months. If the contralateral cylinder is in it should be left in and the procedure completed without placing the contralateral cylinder. Implanters should be aware that modeling for Peyronie's disease increases the risk of perforation to approximately 4 % [30]. Additional support at the fossa navicularis with the surgeons thumb during modeling may reduce this risk.

The reservoir is placed blindly into the retroperitoneum with the penoscrotal approach. To avoid blind placement of the reservoir it can be placed into the retroperitoneum through a Gibson like lateral incision [31]. There is a risk of vascular, bowel, and bladder injury. Due to the peritoneal incision with robotic prostatectomy that is not reapproximated there is theoretically an increased risk of vascular and bowel complications. These concerns have prompted many implanters to utilize ectopic placement of the reservoir. After piercing the back wall of the inguinal ring the reservoir is situated between the abdominal muscles and the transversalis fascia. Higher ectopic placement of the reservoir can be facilitated by use of a long ring clamp or a lung grasper [32]. Concerns about ectopic placement of the reservoir include: noticeable, bulge, autoinflation and migration. The AMS Conceal Reservoir and the Coloplast CL reduce the risk of palpable bulge.

There has been increased interest in the infrapubic approach with a smaller incision described by Perito. A 3 cm transverse infrapubic incision is made which is significantly smaller than infrapubic incisions for prosthesis have been historically. Without a scrotal incision, he reports that 82 % of his patients are sexually active at 4 weeks [33]. Table 15.1 lists several intraoperative scenarios and situations and potential etiologies and solutions.

Complications of IPP

Infection

IPP infections have been dramatically reduced with the advent of infection retardant coatings and improved surgical technique. AMS introduced the Inhibizone coating containing Minocycline and Rifampin. This combination covers *staphylococcus epidermidis*, the organism most commonly cultured from infected implants. The only indication for using a non-coated AMS implant is tetracycline allergy. In 2003, Coloplast added a hydrophilic coating which allows for the absorption of water soluble antibiotics. The infection rate for first time coated and uncoated implants is 2 and 4 %, respectively. Use of a coated implant can reduce the 8–10 % infection rate in revision cases to 2–3 % [34–42]. Preoperative antibiotic prophylaxis should consist of an aminoglycoside plus either vancomycin or a 1st/2nd generation cephalosporin [43]. Increasing postoperative pain is concerning for infection, especially if the pain is improved by the administration of a single dose of antibiotic.

Bacteria that attach to the surface of the implant secrete adhesions molecules which irreversibly bind them to the implant. The bacteria secrete self-preserving polymers and matrix which are capable of protecting the bacteria at 46 h. Bacteria within a biofilm are essentially impervious to phagocytic and cell mediated immunity [44].

Device infection in the era of non-coated implants typically presented relatively late, at least more than 2 months after surgery. Systemic symptoms, fever and severe leukocytosis, were typically absent in prosthesis infection. It was during this era that the concept of prosthesis salvage was developed. Mulcahy reported 84 % success when reimplanting a prosthesis after explant of the infected device and washout. Although fewer infections have developed in the era of coated implants, now patients are presenting earlier and with system illness. Cultures for *Staphylococcus aureus*, *Enterococcus*, and *Pseudomonas* are becoming the predominant offenders [45]. Salvage procedures are less appropriate in the setting of more severe infection.

Table 15.1 Safety checks and intraoperative scenarios

Considerations and/or scenario	Etiology/rationale	Solution
Safety check: timely and correct antibiotics, surgeon and patient skin prep, Dip for Coloplast devices ready	AUA antibiotics best practice statement Literature for skin preparation and Coloplast Dip	Standardized improvement processes
Urethral/spongiosal injury on initial dissection	No urethral catheter, previous scrotal surgery	Close injury in two layers, leave catheter 3–5 days, continue with implant
Difficulty with corporal dilation	Wrong surgical plane, fibrosis: worse distal from priapism and proximal from previous infection or vascular insufficiency	Deepen incision into corporotomies, extend corporotomy length, use depth and angle of already dilated corporal side if available
Safety check: assess proximal dilation with two dilators (goalpost test—image 1)	Dilators should be same depth same angle	If asymmetry either inadequate dilation on one side or perforation of other
Proximal corporal perforation	Vigorous dilation with small caliber dilators, fibrosis from prior case, incorrect dilation angle (typically too medial) (image 3)	Avoid by lateral dilation at crura, account for patient positioning (Trendelenberg etc.), rear tip extender sling [64] and continue
Distal corporal perforation (not urethra)	Vigorous dilation with small caliber dilator	Close under direct vision (distal counter incision)
Safety check: irrigation of corpora distally	Assess for occult distal urethral injury and symmetry of corporal expansion	If fluid out urethra, urethra is perforated (image 2)
Urethral perforation from dilation	Vigorous dilation with small caliber dilator medially	Abort case, may leave one cylinder in place if already present
Urethral injury from modeling (risk 3–4%) [58]	Glans not protected, modeling multiple times, oversized cylinder	Abort case, may leave one cylinder in place if already present but assess for injury with nasal speculum in urethra
Safety check: corporal measurements within 1 cm of another	Asymmetry can result from inadequate dilation or perforation	Redilate short side, implant equal cylinder length to avoid postoperative curve
Difficulty with placement of cylinders	Unrecognized proximal crossover, corporal fibrosis from previous surgery, patient anatomy	Repeat field goal test, leave dilator in one corpora with placement of other, use narrow device if unable to dilate to >10
Distal implant puncture—often unrecognized	Needle crossover distally injuring contralateral cylinder	Stay lateral (visibly deform penis) with initial dilation and Furlow, Pass both needles before seating device distally

(continued)

Table 15.1 (continued)

Considerations and/or scenario	Etiology/rationale	Solution
Safety check: ensure bladder empty prior to standard reservoir placement	Decompress bladder	
Difficulty piercing fascia for standard reservoir placement	Prior surgery (hernia, RRP, Robot RRP), patient age/musculature/contraction, Inadequate upward traction on external ring with retractor	Consider ectopic placement, consider counter-incision
Blood in catheter	Bladder injury, Foley irritation	Perform cystoscopy, consider cystogram
Bladder injury	Reservoir placement with full bladder, removal of old reservoir	Extend incision remove reservoir and repair bladder, place reservoir on opposite side
Slow persistent bleeding from reservoir site	Injury to spermatic cord or small veins vs. iliac injury	Pressure, hemostatic agents, inflate reservoir and later deflate to assess hemostasis
Vigorous bleeding from reservoir site	Occult pelvic vessel injury from reservoir placement, removal of adherent old reservoir	Equanimity, inform anesthesia and vascular surgery, pressure, hemostatic agents, consider counter incision
Difficulty retrieving reservoir—infected implant	Previous unorthodox placement	Counter incision, carefully follow tubing with electrocautery
Difficulty retrieving reservoir—non-infected implant	Previous unorthodox placement	Surgeon judgement: counter incision vs. drain and retain strategy
Safety check: assess for back pressure after reservoir filled to desired volume	If back pressure exists, reservoir may be folded on itself, or space inadequately developed—both may cause auto-inflation	Ensure junction of reservoir and tubing is at external ring/straight; temporarily over-inflate, leave for 10–15 min, reassess pressure
Tubing length for pump too short	Corporotomies relatively distal, wrong cylinder size selected	Reassess measurements and cylinder selection, add rear-tip extenders, make second corporotomy for tubing exit
Safety check: cycle device multiple times to ensure functionality and cosmesis	Rule out occult device puncture; assess for Peyronie's; inspect corporal closures, assess for subtle deformity (crossover: images 4)	Replace device/damaged component; modeling vs. other Peyronie's techniques; reposition cylinders with dilator in place on contralateral side
Glans hypermobile with device fully inflated	Patient anatomy, inadequate dilation distally, cylinder undersized	Reassess dilation and cylinder selection. Avoid fixation at time of initial surgery, glans will often become fixed with healing
Poor hemostasis with standard operative maneuvers	Patient anticoagulation, non-vascular ED, revision case	Consider drain, leaving device inflated, tighter corporotomy closure, compressive dressing

Mechanical Failure

Early in the history of penile prosthesis placement malleable implants were more popular than inflatable prosthesis due to the higher mechanical failure rates associated with the latter. Mechanical failure can be due to a leak from device components, tubing fracture, connector disruption, tubing kinking, or cylinder aneurysm. Multiple series show device survival at 5 years ranging from 83.9 to 93.7 % [5, 6, 46–48]. Ten year studies with the AMS CX/CXM and Ultrex showed 78.3 and 81.2 % of devices free of mechanical failure [49]. In a large series of 2.384 cases with four different device models Wilson et al. showed freedom from mechanical failure rates of 79.4 and 71.2 % at 10 and 15 years, respectively [50].

Revision Surgery with Scarred Corporal Bodies

Placement of cylinders into scarred corporal bodies can be exceedingly difficult. Corporal fibrosis can result from a history of priapism, severe vascular insufficiency, or following explant of an infected prosthesis. The difficulty lies in dilating the scarred corporal body. Typically the fibrosis is worse proximally after explant of an infected device and distally in patient with a history of priapism. Patients with a history of explant for an infected prosthesis also suffer from penile shortening. Scarred corporal bodies often prevent dilation with tradition instruments [51].

Options to create an adequate space in this setting include extensive corporal resection which can require coverage with a biologic agent (SIS). Implant survival is decreased if such manipulation is necessary [52]. Introduction of carvernotomes aided in dilation in this situation. The Carrion–Rossello cavernotomes are sized from 9 to 12 mm. First a wide corporotomy is made to allow sufficient space for the cavernotome to engage. The device is advanced with an oscillating motion. The cavernotome is withdrawn which allows the teeth to open a channel [53]. After the space is dilated, a prosthesis with a narrower base, such as the AMS 700 CXR or narrow based Coloplast, is often required. Despite successful device implantation such patients are frequently disappointed by the loss of length that usually accompanies this fibrosis.

SST

SST deformity is when the glans penis is not in the appropriate anatomic position with the penile prosthesis inflated. It is associated with difficulty in penetration and device dissatisfaction. This can result from an undersized cylinder, lack of distal corporal dilation or a hypermobile glans. If it results from an undersized cylinder or lack of distal corporal dilation, this is appropriately corrected by a revision in which the distal corporal body is dilated an appropriately sized cylinder is placed. If the SST deformity results from a hypermobile glans, then realigning the glans with the shaft of the penis will allow for proper penetration as described by Mulhall [54]. The glans is mobilized through a dorsal subcoronal incision and then repositioned more proximally on the corporal body using non-absorbable suture.

Distal Extrusion

Another complication of penile prosthesis involves the distal extrusion of the cylinders through the corpus cavernosum. This complication occurs most often in those with reduced penile sensation; however, it can result from overly aggressive distal dilation. Oversizing of the cylinder length may also contribute. Mulcahy described using the fibrous capsule for repair. After removal of the original device, a hemicircumcising incision is made on the side where the device extruded. The lateral aspect of the fibrous capsule is incised. The medial wall of the capsule is then incised and a new plane of dissection is developed behind the medial wall of the capsule. This allows for a new tract for the cylinder. The new cylinder is placed in the standard fashion using the Furlow device. The capsule is then closed, providing an extra layer of coverage for the device. When he originally described his

technique in 1999 he left the original cylinders in place. Now it is standard to change out the device components.

Other techniques have been described. Carson examined his own series comparing using the capsule for a rerouting versus using Goretex Windsock [55]. Operative time was increased for the windsock compared to rerouting. There was a device infection requiring explantation in the Goretex group while there was not in the rerouting group. Although the numbers were small there was the suggestion that the windsock repair resulted in more pain and a higher percentage of patients had a recurrence with the Windsock.

Lue has described a separate technique where a transglanular incision is made over the tip of the cylinder. The fibrous capsule is incised and a suture is passed through the eyehole of the prosthesis. This suture is tied to the fibrous capsule contralateral the side of the extrusion [56].

Reservoir Herniation

Reservoir herniation is an uncommon complication which occurs almost solely in implants placed through a penoscrotal incision [57]. It is most commonly related to significant increases in intraabdominal pressure early in the postoperative period, usually related to vigorous coughing of vomiting. Occasionally it may be secondary to an error in surgical technique. There is no need for correction unless the patient finds it bothersome. There are two reasons to delay immediate surgical correction of reservoir herniation. First the patient may find the herniation less bothersome after the fibrous capsule has formed around the reservoir. Second, the capsule can be used in the correction of the problem.

For correction the surgeon makes an incision over the herniated reservoir and the planes dissected until the fibrous capsule is encountered. The anterior wall of the capsule is first incised. After displacement of the reservoir the posterior wall of the capsule is now entered. After going through the posterior wall of the capsule the transversalis fascia is encountered. Now the surgeon can develop sufficient room in the space of Retzius for placement of the reservoir. The anterior and posterior walls of the capsule are closed to reinforce the appropriate placement.

Postoperative Care

Patients can be discharged home the same day of surgery or the following day. Patients are seen for a wound check and then are taught to the cycle the device between 4 and 6 weeks. Intercourse typically commences within 1–2 months. Frequent reassurance is typically needed for the patients with concerns. Early daily device cycling is important to prevent a contracted capsule from developing around the cylinders. Although up to 20% of patients rarely or never use the device, most patients would choose to undergo the operation again. Patients with complications should be seen more frequently than is typical to prevent the development of a negative relationship.

References

1. Lindeborg L, Fode M, Fahrenkrug L, et al. Satisfaction and complications with the Titan® one-touch release penile implant. Scand J Urol. 2014;48(1):105–9.
2. Bettocchi C, Palumbo F, Spilotros M, et al. Patient and partner satisfaction after AMS inflatable penile prosthesis implant. J Sex Med. 2010;7:304.
3. Natali A, Olianas R, Fisch M. Penile implantation in Europe: successes and complications with 253 implants in Italy and Germany. J Sex Med. 2008;5:1503.
4. Brinkman MJ, Henry GD, Wilson SK, et al. A survey of patients with inflatable penile prostheses for satisfaction. J Urol. 2005;174:253.
5. Montorsi F, Rigatti P, Carmignani G, et al. AMS three-piece inflatable implants for erectile dysfunction: a long-term multi-institutional study in 200 consecutive patients. Eur Urol. 2000;37:50–5.
6. Carson CC, Mulcahy JJ, Govier FE. Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. J Urol. 2000;164:376–80.
7. 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.
8. Garber BB. Mentor Alpha 1 inflatable penile prosthesis: patient satisfaction and device reliability. Urology. 1994;43:214.

9. Goldstein I, Newman L, Baum N, et al. Safety and efficacy outcome of mentor alpha-1 inflatable penile prosthesis implantation for impotence treatment. J Urol. 1997;157:833.
10. Goldstein I, Bertero EB, Kaufman JM, et al. Early experience with the first pre-connected 3-piece inflatable penile prosthesis: the Mentor Alpha-1. J Urol. 1993;150:1814.
11. Bernal RM, Henry GD. Contemporary patient satisfaction rates for three-piece inflatable penile prostheses. Adv Urol. 2012;2012:707321.
12. Shaw T, Garber BB. Coloplast Titan inflatable penile prosthesis with one-touch release pump: review of 100 cases and comparison with genesis pump. J Sex Med. 2011;8:310–4.
13. Knoll LD, Henry G, Culkin D, Ohl DA, Otheguy J, Shabsigh R, Wilson SK, Delk IJ. Physician and patient satisfaction with the new AMS 700 momentary squeeze inflatable penile prosthesis. J Sex Med. 2009;6(6):1773–8.
14. Hammerich K, Humphrey JE, Bennett NE, Jr. Anticoagulative therapy is not a contraindication for penile prosthesis implantation. Presented at the World Meeting on Sexual Medicine. Chicago, IL; 2012. Abstract 157. Accessed 26–30 Aug 2012.
15. http://www.coloplast.us/titan-otr-en-us.aspx#section=product-description_3.
16. Rajpurkar A, Dhabuwala CB. Comparison of satisfaction rates and erectile function in patients treated with sildenafil, intracavernous prostaglandin E1 and penile implant surgery for erectile dysfunction in urology practice. J Urol. 2003;170:159.
17. Trost LW, Baum N, Hellstrom WJ. Managing the difficult penile prosthesis patient. J Sex Med. 2013;10:893.
18. Mulhall JP, Jahoda A, Aviv N, et al. The impact of sildenafil citrate on sexual satisfaction profiles in men with a penile prosthesis in situ. BJU Int. 2004;93:97.
19. Miranda-Sousa A, Keating M, Moreira S, Baker M, Carrion R. Concomitant ventral phalloplasty during penile implant surgery: a novel procedure that optimizes patient satisfaction and their perception of phallic length after penile implant surgery. J Sex Med. 2007;4(5):1494–9.
20. Yeung LL, Grewal S, Bullock A, et al. A comparison of chlorhexidine-alcohol versus povidone-iodine for eliminating skin flora before genitourinary prosthetic surgery: a randomized controlled trial. J Urol. 2013;189:136.
21. Eid JF, Wilson SK, Cleves M, et al. Coated implants and "no touch" surgical technique decreases risk of infection in inflatable penile prosthesis implantation to 0.46%. Urology. 2012;79:1310.
22. Eid JF, Wilson SK, Cleves M, Salem EA. Coated implants and "no touch" surgical technique decreases risk of infection in inflatable penile prosthesis implantation to 0.46%. Urology. 2012;79(6):1310–5.
23. Henry G, Hsiao W, Karpman E, Bella AJ, Carrion R, Jones L, Christine B, Eisenhart E, Cleves MA, Kramer A. A guide for inflatable penile prosthesis reservoir placement: pertinent anatomical measurements of the retropubic space. J Sex Med. 2014;11(1):273–8.
24. Wilson SK, Delk JR, Henry GD, Siegel AL. New surgical technique for sphincter urinary control system using upper transverse scrotal incision. J Urol. 2003;169:261–4.
25. Szostak MJ, DelPizzo JJ, Sklar GN. The plug and patch: a new technique for repair of corporal perforation during placement of penile prostheses. J Urol. 2000;163(4):1203–5.
26. Mooreville M, Adrian S, Delk 2nd JR, Wilson SK. Implantation of inflatable penile prosthesis in patients with severe corporeal fibrosis: introduction of a new penile cavernotome. J Urol. 1999;162(6):2054–7.
27. Wilson SK. Rear tip extender sling: a quick and easy repair of crural perforation. J Sex Med. 2010;7:1052.
28. Mulcahy JJ. Prevention and correction of penile implant problems. AUA Update Series 1994;13:lesson 27.
29. Wilson SK. Pearls, perils and pitfalls of prosthetic urology. A troubleshooting guide for physicians. Fort Smith, Arkansas: Calvert McBride, Inc.; 2008.
30. Wilson SK, Cleves MA, Delk 2nd JR. Long-term followup of treatment for Peyronie's disease: modeling the penis over an inflatable penile prosthesis. J Urol. 2001;165(3):825–9.
31. Hartman Jr RJ, Helfand BT, McVary KT. Outcomes of lateral retroperitoneal reservoir placement of three-piece penile prosthesis in patients following radical prostatectomy. Int J Impot Res. 2010;22:279.
32. Morey AF, Cefalu CA, Hudak SJ. High submuscular placement of urologic prosthetic balloons and reservoirs via transscrotal approach. J Sex Med. 2013;10:603.
33. Perito PE. Minimally invasive infrapubic inflatable penile implant. J Sex Med. 2008;3:27.
34. Mulcahy JJ, Carson 3rd CC. Long-term infection rates in diabetic patients implanted with antibiotic-impregnated versus nonimpregnated inflatable penile prostheses: 7-year outcomes. Eur Urol. 2011;60:167.
35. Bishop JR, Moul JW, Sihelnik SA, et al. Use of glycosylated hemoglobin to identify diabetics at high risk for penile periprosthetic infections. J Urol. 1992;147:386.
36. Jarow JP. Risk factors for penile prosthetic infection. J Urol. 1996;156:402.
37. Wilson SK, Delk 2nd JR. Inflatable penile implant infection: predisposing factors and treatment suggestions. J Urol. 1995;153:659.
38. Wilson SK, Zumbe J, Henry GD, et al. Infection reduction using antibiotic-coated inflatable penile prosthesis. Urology. 2007;70:337.
39. Radomski SB, Herschorn S. Risk factors associated with penile prosthesis infection. J Urol. 1992;147:383.
40. Serefoglu EC, Mandava SH, Gokce A, Chouhan JD, Wilson SK, Hellstrom WJ. Long-term revision rate due to infection in hydrophilic-coated inflatable

penile prostheses: 11-year follow-up. J Sex Med. 2012;9(8):2182–6.
41. Carson 3rd CC, Mulcahy JJ, Harsch MR. Long-term infection outcomes after original antibiotic impregnated inflatable penile prosthesis implants: up to 7.7 years of followup. J Urol. 2011;185(2):614–8.
42. Nehra A, Carson 3rd CC, Chapin AK, Ginkel AM. Long-term infection outcomes of 3-piece antibiotic impregnated penile prostheses used in replacement implant surgery. J Urol. 2012;188(3): 899–903.
43. Wolf Jr JS, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol. 2008;179:1379.
44. Silverstein AD, Henry GD, Evans B, Pasmore M, Simmons CJ, Donatucci CF. Biofilm formation on clinically noninfected penile prostheses. J Urol. 2006;176(3):1008–11.
45. Kava BR, Kanagarajah P, Ayyathurai R. Contemporary revision penile prosthesis surgery is not associated with a high risk of implant colonization or infection: a singlesurgeon series. J Sex Med. 2011;8:1540.
46. Deuk Choi Y, Jin Choi Y, Hwan Kim J, et al. Mechanical reliability of the AMS 700CXM inflatable penile prosthesis for the treatment of male erectile dysfunction. J Urol. 2001;165:822–4.
47. Daitch JA, Angermeier KW, Lakin MM, et al. Long-term mechanical reliability of AMS 700 series inflatable penile prostheses: comparison of CX/CXM and Ultrex cylinders. J Urol. 1997;158:1400–2.
48. Dubocq F, Tefilli MV, Gheiler EL, et al. Long-term mechanical reliability of multicomponent inflatable penile prosthesis: comparison of device survival. Urology. 1998;52:277–81.
49. Dhar NB, Angermeier KW, Montague DK. Long-term mechanical reliability of AMS 700CX/CXM inflatable penile prosthesis. J Urol. 2006;176:2599–601.
50. Wilson SK, Delk JR, Salem EA, Cleves MA. Long term survival of inflatable penile prostheses: single surgical group experience with 2,384 first time implants spanning two decades. J Sex Med. 2007;4:1074–9.
51. Martínez-Salamanca JI, Mueller A, Moncada I, et al. Penile prosthesis surgery in patients with corporal fibrosis: a state of the art review. J Sex Med. 2011;8:1880.
52. Boyd SK, Martins FE. Simultaneous Ultrex penile prosthesis reimplantation and Gore-Tex grafting corporoplasty: functional outcomes of a surgical challenge. J Urol. 1995;153(Suppl A):359.
53. Wilson SK, Delk JR, Terry T. Improved implant survival in patients with severe corporal fibrosis: a new technique without the necessity of grafting. J Urol. 1995;153(Suppl A):359.
54. Mulhall JP, Kim FJ. Reconstructing penile supersonic transporter (SST) deformity using glanulopexy (glans fixation). Urology. 2001;57(6):1160–2.
55. Carson CC, Noh CH. Distal penile prosthesis extrusion: treatment with distal corporoplasty or Gortex windsock reinforcement. Int J Impot Res. 2002;14(2):81–4.
56. Shindel AW, Brant WO, Mwamukonda K, Bella AJ, Lue TF. Transglanular repair of impending penile prosthetic cylinder extrusion. J Sex Med. 2010;7(8):2884–90.
57. Sadeghi-Nejad H, Sharma A, Irwin RJ, Wilson SK, Delk JR. Reservoir herniation as a complication of three-piece penile prosthesis insertion. Urology. 2001;57(1):142–5.
58. Steidle J and Mulcahy JJ: Erosion of penile prostheses: a complication of urethral catheterization. J Urol 1989. 142:736.

16 Endovascular Approaches to Penile Arterial Revascularization for Vasculogenic Erectile Dysfunction

Joshua D. Ring, Aye A. Lwin, and Tobias S. Köhler

Introduction

Erectile dysfunction (ED) is a common medical problem affecting a large and growing population of males around the world. Defined as a recurring inability to achieve and maintain an erection satisfactory for sexual intercourse [1], the condition currently affects approximately 50 % of men aged 45–75 [2], estimated to affect 150 million males worldwide with projections of up to 322 million by 2025 [3]. Although the condition is not life-threatening in and of itself, the successful management of ED is strongly correlated with quality of life improvement [4, 5]. Current medical therapies aim to correct or reverse underlying etiologies, with subsequent, residual ED being treated with oral phosphodiesterase-5 inhibitors (PDE5i). This pharmacotherapy aims to increase penile blood flow via cavernosal smooth muscle relaxation and improve endothelial function. However, greater than 50 % of men have a suboptimal response to PDE5i therapy [6]. PDE5i have waning efficacy in men as their underlying ED pathologies progress and contraindicated in another proportion of men. The ensuing treatments available for ED involve more invasive endeavors including vacuum pumps, intraurethral suppositories, intracavernosal injections (ICI) with vasodilators, and penile prostheses. There exists a need for additional effective mechanisms for treatment of ED [7], particularly those that are less cumbersome or invasive compared to traditional second- and third-line approaches.

ED and coronary artery disease (CAD) share many common cardiovascular risk factors, including age, diabetes, hypertension, dyslipidemia, and tobacco use [8–10]. ED has been shown to be a preceding symptom of CAD and a risk factor for development of cardiovascular disease [11], with up to 70 % of males experiencing new-onset angina and angiographically confirmed CAD having a previous past medical history significant for ED [12–14]. Shared underlying etiologies between CAD and ED relate to atherosclerosis, endothelial dysfunction, and diminished hemodynamics. Prior angiographic studies have observed significant obstructive atherosclerotic disease in iliac, internal pudendal, and cavernosal arteries in males with ED [15–17]. Documentation rates of men with CAD and concurrent ED have been seen as high as 75 % [18, 19]. Although the causes for ED are multifactorial, the vasculogenic etiology is the most predominant, with one study documenting that it may account for >80 % of cases of ED [20] with the

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arteriogenic subtype present in greater than 55 % of males with ED [21]. Furthermore, of the 50 % of males who had suboptimal responses to PDE5i pharmacotherapy, 90 % have been shown to have angiographically severe penile arterial insufficiency (PAI) [19]. Thus, there exists a need for the development of minimally invasive penile arterial revascularization therapies for the treatment of vasculogenic ED. Chapter 9 in this volume delves deeper into the connection between cardiovascular disease and the diagnosis and treatment of ED.

Endovascular revascularization via transluminal balloon angioplasty has shown successful results with short-term improvement of erectile function [22], and the ZEN (Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with Suboptimal Response to PDE5 Inhibitors) trial proved the safety and feasibility of peripheral endovascular drug-eluting stents [23]. However, therapies targeting penile arterial vascularization have not yet been recommended by the American Urological Association (AUA) in the treatment guidelines for ED and remain "experimental" [7]. This chapter will discuss the current state of endovascular penile arterial revascularization for vasculogenic erectile dysfunction. This chapter will discuss the current state of endovascular penile arterial revascularization for vasculogenic erectile dysfunction. We will aim to summarize background anatomy and physicology, etiologies of ED, and the ZEN trial of pudendal artery stents. Last, we focus on endovascular stent restenosis, available imaging modalities, recent work on transluminal balloon angioplasty of the penile arterial supply, and future directions for the field of endovascular penile arterial revascularization for the treatment of vasculogenic erectile dysfunction.

Vasculogenic Erectile Dysfunction

Historically, erectile dysfunction was predominantly thought to be a psychogenic disorder, with Kinsey et al. in 1948 first portraying the phenomena to be due to an age-related decline in function [24]. This portended to be the principal, etiological theory for its manifestation until the late twentieth century, whereupon we know it as an organic and physiological breakdown of the penile neurovasculature. Normal sexual function requires the appropriate interplay of hormonal, neurological, vascular, and psychological systems. Penile erection is a complex neurovascular phenomenon requiring the coordination of penile vasculature dilation via smooth muscle relaxation, increased intracavernosal blood flow, and appropriate veno-occlusive function. Vasculogenic erectile dysfunction is the most common and prevalent of all its etiologies, among hormonal, neurological, psychological, drug-induced, and trauma pathways. Erectile dysfunction can stem from impaired cavernosal smooth muscle relaxation, diminished arterial inflow, and veno-occlusive dysfunction. These multifactorial components ultimately lead to hypoxemia and the underlying common pathway of endothelial dysfunction [25]. Vasculogenic ED can be categorized into veno-occlusive or cavernosal, arteriogenic, and mixed. Veno-occlusive disease is the most common of the three and is characterized by increased venous outflow of subtunical vessels causing impaired engorgement and penile rigidity [26]. Common causes for veno-occlusive ED include diabetes, aging, Peyronie's disease, and trauma, all of which cause structural changes [27–29].

Penile arterial insufficiency is caused by occlusion or stenosis of arterial beds from the common iliacs to its downstream branches (Fig. 16.1a, b). Any common risk factors for atherosclerosis can induce this process including hypercholesterolemia, hypertension, and tobacco use. Vasculogenic erectile dysfunction is an early manifestation of a macrovascular, atherogenic, systemic disease process linked by endothelial dysfunction, with the severity of ED linked angiographically to the extent of CAD [30]. Thus, as an extrapolation of the compiled data showing ED to be a precursor to CAD, the "artery size hypothesis" puts forth that if it is believed that the atherosclerotic process occurs at the same pace throughout the arterial system, the arteries with smaller diameters will be ini-

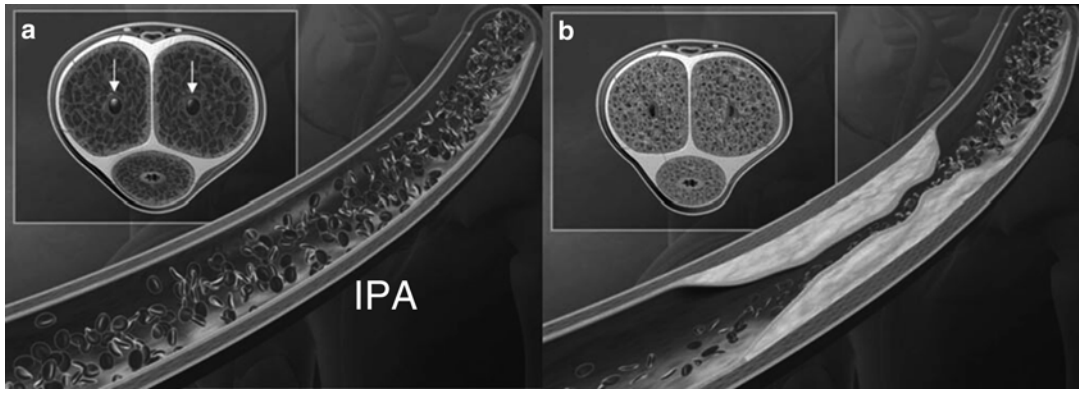

Fig. 16.1 (**a**, **b**) Arterial insufficiency resulting in vasculogenic erectile dysfunction. (**a**) Normal arterial inflow via the internal pudendal artery resulting in cavernosal engorgement. Arrows noting paired cavernosal arteries in penile shaft cross-section. (**b**) Atherosclerotic stenosis of penile arterial inflow resulting in insufficient intracavernosal pressures and vasculogenic erectile dysfunction. (Used with permission from Rogers JH, et al. Internal pudendal artery stenoses and erectile dysfunction: Correlation with angiographic coronary artery disease. Catheter Cardiovasc. Interv. 2010; 76(6):882–887)

tially symptomatic [31]. Thus, the small-diameter helicine arteries in the penis become damaged early in the atherogenic process, in comparison to larger-diameter coronary arteries. Montorsi et al. support this hypothesis in a study that found 71 % men to show signs of sexual dysfunction before the onset of CAD symptoms [14]. However, vasculogenic ED cannot be completely accounted for by atherosclerosis, as endothelial dysfunction seems to be the common denominator involved in its complex pathogenesis [32]. Arterial insufficiency initiates a cytotoxic cascade from tissue hypoxia that involves the endothelium, cavernosal smooth muscle cells, and neuro-microvasculature which ultimately results in fibrosis [33, 34]. Cavernosal fibrosis and impaired smooth muscle relaxation can also be caused iatrogenically by radiation therapy and surgery, as well as from priapism and trauma or any distortion of the tissue architecture which often lead to venous leak [35, 36].

The integrity of arterial sufficiency necessary for erectile function was first observed by the French surgeon René Leriche who described the "Leriche triad" in 1923 for aortoiliac occlusion which included buttock and lower extremity claudication, gluteal atrophy, and impotence caused by inadequate perfusion of the corporal bodies [37]. In 1969, this observation was again documented as 70 % of men with aortoiliac occlusion were found to have ED [38], and restoration of erectile function was observed after bilateral endarterectomy of occluded internal iliac arteries [39]. Angiographic and histologic data from 1973 correlated penile arterial insufficiency with ED [40, 41]. Arteriography for ED was first used in 1976 by Romieu and Ginestie [42], but Michal et al. in 1978 first coined "phalloarteriography" in his angiographic demonstration of arterial occlusive disease in the vessels supplying the corpus cavernosum in males with ED [43]. Valji et al. in 1988 documented distal internal pudendal and proximal penile artery stenoses as common sites for occlusive disease [44]. Subsequent investigators also documented these distal arterial stenoses in the internal pudendal artery (IPA), though the enrolled patients were young males with ED secondary to pelvic trauma [17]. A review from 2013 compiled the ten studies to date that assessed penile arterial circulation in 629 males with ED, finding PAI ranges between 37 and 79 % with an average incidence of 76 % [21]. This may be an overestimation in comparison to the general population due to the selection bias inherent with the majority of enrolled patients having concurrent CAD.

Historically, from 1973 up until the early 2000s, penile revascularization procedures were only utilized for acute pelvic trauma cases in young men with vasculogenic erectile dysfunction, using an epigastric artery to deep dorsal vein or cavernosal artery bypass, with initial success rates ranging from 50 to 70 %. However, these patients experienced high, long-term failure rates related to vessel leak and arteriogenic disease [36]. Only 4 of 31 such publications with 50 total patients met peer-reviewed criteria set by the AUA guidelines that were due to heterogeneous surgical approaches, lack of randomization, and short follow-ups [21]. During the 1980s and 1990s, percutaneous transluminal angioplasty without stents through the contralateral femoral approach was performed for the treatment of ED in young to middle-age men. These studies mostly focused on the larger iliac arteries, with only three reports directed at the IPA [45]. Success rates averaged 55 % in a total of 65 patients and high recurrence rates likely secondary to restenoses [46–51]. These case reports enrolled patients with blunt pelvic trauma who had short-term follow-ups and no pre-procedural evaluations for vasculogenic ED. A summary of these case reports and more recent studies can be found below (Table 16.1).

Table 16.1 Pelvic arterial inflow studies for erectile dysfunction

Study	*n*	Anatomical variations of internal pudendal and accessory arteries	Location of stenosis
Michal [43]	30	N/A	100 % cavernosal arteries
Herman [90]	35	N/A	100 % IPA
Struyven [91]	14	N/A	50 % IPA
Huguet [64]	200	85 % from ILA, 65 % from gluteo-pudendal artery	Not described
Buvat [68]	29	N/A	37 % proximal IPA 48 % distal disease (perineal and cavernosal arteries
Bruhllman [66]	24	Accessory pudendal artery from superior vesical, urachal, and obturator arteries	71 % IPA 24 % mid-segment of IPA 59 % bilateral IPA 100 % deep and dorsal penile arteries
Gray [71]	73	21 % with accessory pudendal arteries, 14 % of which were unilateral and 7 % bilateral	44 % ILA or proximal IPA 44 % distal IPA or cavernosal arteries
Nessi [92]	44	N/A	79 % IPA 20 % occlusion of IPA or bilateral disease 52 % single vessel occlusion or multiple Lesions in a single vessel
Valji [44]	57	N/A	19 % ILA 70 % IPA 40 % distal disease 56 % intrapenile disease
Rosen [10]	170	N/A	Cavernosal arteries in the majority
Rogers [53]	10	N/A	90 % IPA
Wang [83]	25	N/A	59 % common penile artery 38 % dorsal penile artery 3 % ostium of the cavernosal artery
Total[a]	655		IPA disease, 144/259 (56 %) Small vessel disease, 303/488 (62 %)

ILA internal iliac artery, *IPA* internal pudendal artery, *N/A* not applicable

Adapted with permission from Philip F, Shishehbor MH. Current state of endovascular treatment for vasculogenic erectile dysfunction. Curr Cardiol Rep 2013;15(5): 360

[a]Patients from Hugat et al. and Rosen et al. were excluded from the totals due to lack of quantifiable data for degree and location of arterial stenoses

And thus with the paucity of literature, the AUA still considers penile arterial revascularization to be an "experimental" treatment modality for vasculogenic ED. Penile revascularization aims to treat short, isolated stenoses [2, 3] of the internal pudendal and proximal penile arteries, where approximately 70% lesions have been identified to occur. Recent evidence examining pelvic arterial lesions utilizing computed tomographic angiography (CTA) identified 90% lesions to be located in the common penile and internal pudendal arteries in 80 patients with ED. Of these, 30% were limited to the penile artery segments and 15% to the IPA [52]. In Table 16.1 from a 2013 review with updated data, 11 compiled studies assessing PAI with a total summed cohort of 655 males with ED found an incidence of 56% with IPA disease and 62% with more distal small vessel disease [21]. The PANPI (Pelvic Angiography in Non-Responders to Phosphodiesterase-5 Inhibitors) study in 2008 was the first to angiographically correlate CAD and IPA stenosis in patients with ED. IPA atherosclerotic stenoses were found to occur most often in the mid-to-distal IPA and were surprisingly similar in nature to the atherosclerotic narrowing observed in the coronary arteries with slightly smaller but similar luminal diameter sizes [53].

Pudendal Artery Basic Science

Penile erections occur as a neurovascular phenomenon, requiring proper arterial inflow and venous outflow occlusion. The penile circulation arises from the anterior division of the bilateral internal iliac arteries, branches of the common iliac, specifically from inflow of the internal pudendal arteries. The IPA is the largest terminal branch of the internal iliac and the longest named segment of the penile arterial circulation, measuring 15 cm on average from its origin to the base of the penis. It travels infero-posteriorally in a neurovascular bundle with the internal pudendal nerve within the true pelvis, exiting the pelvis along the inferior border of the greater sciatic foramen and emerging across the ischial spine. This landmark is valuable when trying to identify the IPA angiographically as it frequently crosses the femoral head [21]. The IPA then courses posterior (superficial) to the sacrospinous ligament and anterior (deep) to the sacrotuberous ligament, entering the pudendal (Alcock's) canal travelling anteromedial toward the base of the penis. During its course through the canal, it gives rise to the inferior rectal artery which supplies the external anal sphincter. The distal IPA then gives off the perineal artery and becomes the common penile artery, which penetrates through the pelvic floor along with the bulbar urethra [22]. Though intrapenile arterial circulation can be variable, the common penile artery usually splits into the bulbourethral, dorsal, and cavernosal (also known as deep penile artery) branches. These are paired, intrapenile, terminal branches that supply penile tissue and communicate through transverse communications near the base of the penis. This is believed to be an important source of collateral circulation in the presence of unilateral disease [54]. After giving off these terminal branches, the common penile artery then transitions into the dorsal penile artery that extends to the glans supplying the skin and fascia of the penis. The six intrapenile, terminal branches distally join to form a vascular ring at the base of the glans, though most of the glans circulation is derived from the dorsal and bulbourethral arteries. Communicating branches between the cavernosal arteries and between cavernosal and dorsal arteries are common [55]. Figure 16.2 demonstrates the relevant penile blood supply described above.

The cavernosal arteries are the most vital for tumescence, supplying most of the corpora cavernosum. They enter the corpora cavernosum at the crus and extend throughout the shaft while subdividing into helicine arteries that supply the lacunar spaces within the corpora cavernosum and maintain penile rigidity during erections [22]. Filling of these corporal sinusoids, a trabeculated network of smooth muscle, during full erections produces intracavernosal pressures up to 100 mmHg, while during intercourse (rigid erection), it produces suprasystolic pressures up

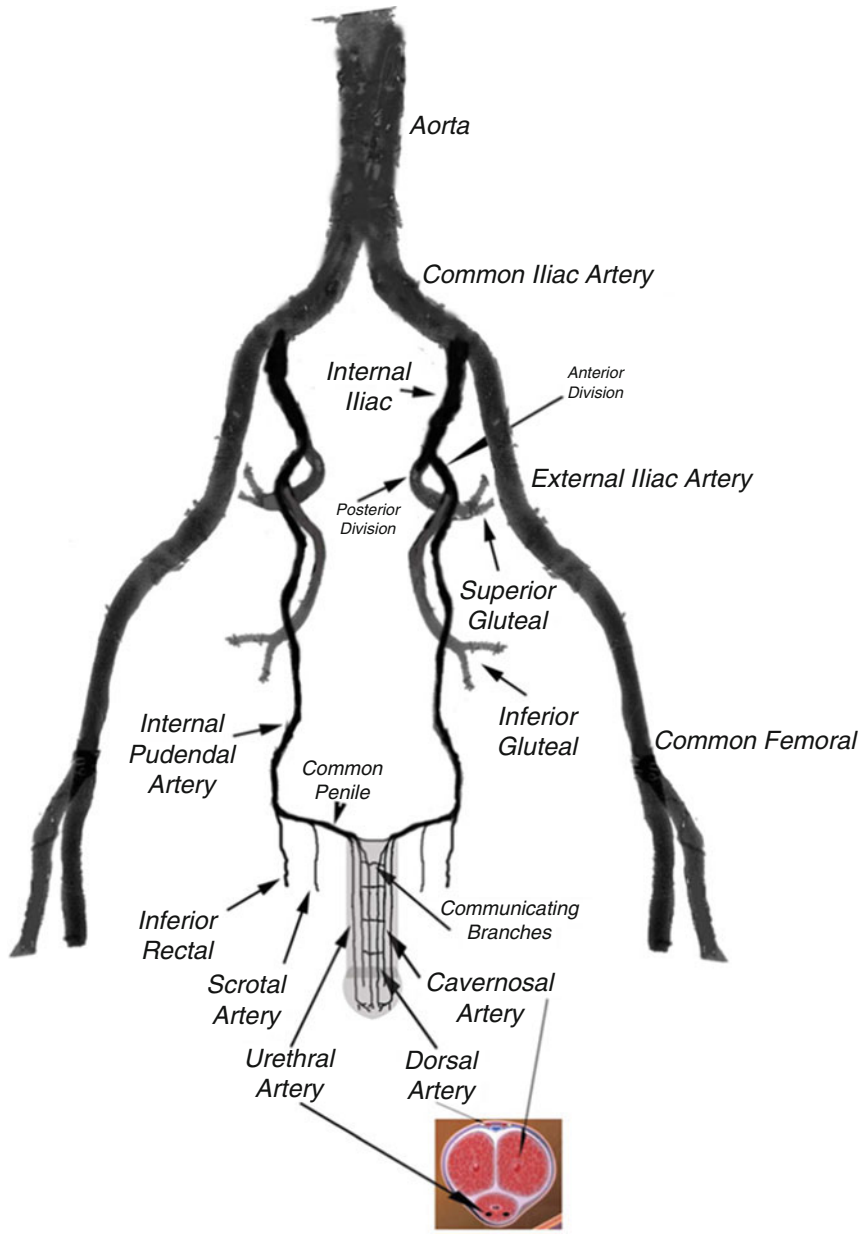

Fig. 16.2 Erectile-related arterial vasculature. (Used with permission from Rogers JH, et al. Endovascular Therapy for Vasculogenic Erectile Dysfunction. Current Treatment Options in Cardiovascular Medicine 2012; 14(2):193–202)

to 200–300 mmHg through smooth muscle cell relaxation of the helicine arteries and ischiocavernosal muscle contraction which propagates rapid blood flow from the IPA into the cavernosal arteries [35, 53]. This vascular bed lacks capillaries, facilitating rapid arterial inflow through the corporal sinusoids during erections and venous outflow via arteriovenous shunting in flaccid states [55–58]. The major site of resistance in vascular beds systemically usually occurs in resistance arteries with diameters less than 100 μm [59], though studies have shown that within the penile circulation, 70 % of total resistance is observed in the pudendal arteries and not the small-diameter cavernosal and intrapenile arterioles. However, for optimization of erectile

function, it has been demonstrated that vasodilation of both the pudendal and intracavernosal arteries needs to occur [60]. Venous drainage through subtunical and emissary veins is limited during erections due to passive external compression from the tunica albuginea surrounding the corpora cavernosum. However, during flaccid states sinusoidal smooth muscle cells of the helicine arteries contract and prevent blood flow, permitting venous drainage through open emissary veins draining distally through the circumflex veins into the deep dorsal vein of the penis and proximally through the crural and cavernosal veins draining into the internal pudendal veins [55]. Thus, arterial inflow stenoses that preclude filling of the corporal bodies, impaired cavernosal smooth muscle relaxation, or veno-occlusive dysfunction incurring venous leakage can all cause vasculogenic ED. See Fig. 16.3.

Morphologically, the IPA is a vessel with a small lumen, relatively equivalent to that of a first-order mesenteric branch, and a thick smooth muscle wall, equivalent to that of a renal artery which has twice the luminal diameter. This morphological distinction of an increased medial layer is necessary to withstand the episodic, suprasystolic pressures incurred during erections due to the rapid arterial influx, though normally under low flow conditions. This requires unique physiologic properties that make the IPA a sensible target for revascularization [61, 62]. Based on Poiseuille's flow mechanics, resistance is proportional to the inverse of the radius raised to the fourth power ($R \propto 1/r^4$). Thus, changes to the luminal diameter of pudendal arteries drastically affect the rate of blood flow. For example, a 10 % decrease in the luminal radius results in a 52 % increase in resistance to arterial inflow [63]. Hannan et al. [61] showed in rats that with aging, significant vascular remodeling occurs in conjunction with an age-related decline in erectile function. This was found to be related to decreased endothelial-mediated relaxation of the IPA, without corresponding morphological changes observed in the mesenteric arteries. These changes also occurred in the IPA to a greater degree than those observed in the aorta and renal arteries. It was hypothesized that the

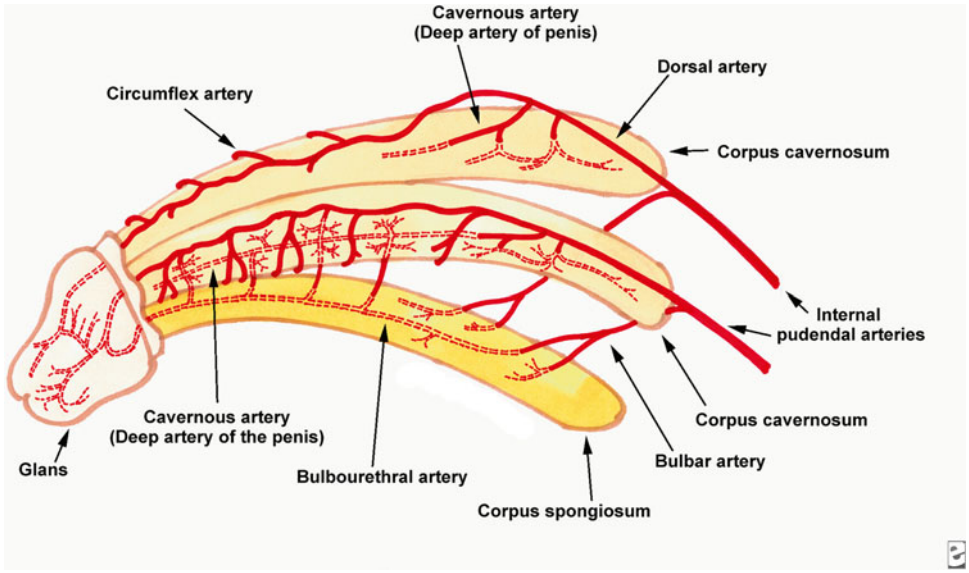

Fig. 16.3 Penile arterial anatomy (Used with permission from Terlecki RP, et al. Phimosis, adult circumcision, and buried penis. Medscape: 2011. Image reprinted with permission from Medscape Drugs & Diseases (http://emedicine.medscape.com/) 2015; available at: http://emedicine.medscape.com/article/442617-overview)

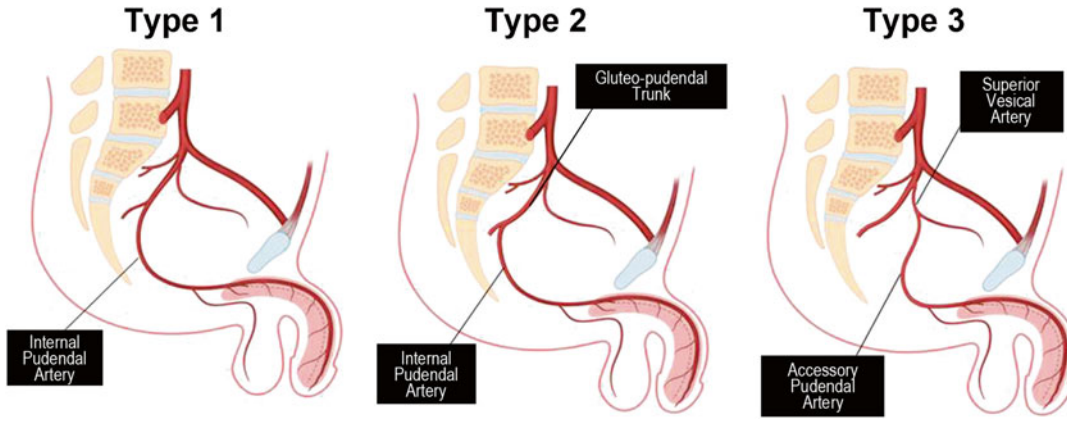

Fig. 16.4 Variations in internal pudendal artery vasculature with classification scheme. Type 1-IPA from internal iliac artery. Type 2-IPA from inferior gluteal artery. Type 3-accessory vessel (here shown originating from superior vesical artery) (Used with permission from Philip F, Shishehbor MH. Current State of Endovascular Treatment of Vasculogenic Erectile Dysfunction. Curr Cardio Rep 2013; 15(5):360)

IPA undergoes "rapid aging" with its increased susceptibility due to its unique physiologic requirements: an episodic, suprasystolic hemodynamic load during erectile responses in comparison to its normal-state low flow condition with minimal metabolic autoregulation.

Anatomically, variations of the IPA have been found to be quite common and have thus been categorized into three types illustrated in Fig. 16.4. In type 1, the IPA originates from the anterior division of the internal iliac which occurs in 30 % of patients. Type 2 classifies the IPA as originating from a gluteo-pudendal trunk from the inferior gluteal artery, occurring in 70 % of patients [64]. Type 3 is classified as an accessory IPA which has been observed in 11 % of patients [65]. Atherosclerosis of the IPA has been shown to be part of a diffuse process, with lesions of the ostial or proximal segments observed in 56 % of cases and 60 % observed in distal (small penile) segments [66, 67]. Multifocal atherosclerotic lesions were more commonly seen in older patients and diabetics [68]. In one clinical study, men with vasculogenic ED were found to have evidence of IPA lesions in 53 % of men [20], while a review from 2013 showed an overall incidence of 56 % [21].

ZEN Trial

The first multi-institutional clinical trial to examine the safety and feasibility of employing internal pudendal artery drug-eluting stents (DES) for the treatment of vasculogenic ED was the Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with the Suboptimal Response to PDE-5 Inhibitors (ZEN) trial published in 2012 [23]. With recruitment methods that focused on urologists finding suitable candidates, 383 subjects were screened, and those with an International Index of Erectile Function 6 (IIEF-6) baseline score <22 were placed into a 4-week run-in phase. IIEF-6 is a modified IIEF utilizing six questions that have been documented to have the highest discriminating power to diagnose ED [69]. The 4-week run-in phase included a 4-week trial of PDE5i and a minimum of four sexual encounters. Those patients with IIEF-6 scores remaining <22 with reported ED in half of their sexual encounters or greater were screened by penile duplex ultrasound with intracavernosal injection. The subjects with adequate peak systolic velocities (PSV) and venous leakage were excluded. Key exclusion criteria also

included patients on nitrates or those with a bleeding disorder. With the aforementioned criteria met, 89 subjects (23 %) qualified to undergo invasive penile arteriography, which aimed to include patients with unilateral or moderate-to-severe bilateral stenoses of the IPA with focal lesions, excluding those with ≥70 % stenoses of non-IPA penile inflow arteries. One-third of patients screened had systemic atherosclerotic disease, and one-third had minimal as observed angiographically and were excluded. A total of 30 subjects (7.8 %) were enrolled in the trial and treated for their penile artery insufficiency via internal pudendal artery stents. See Fig. 16.5.

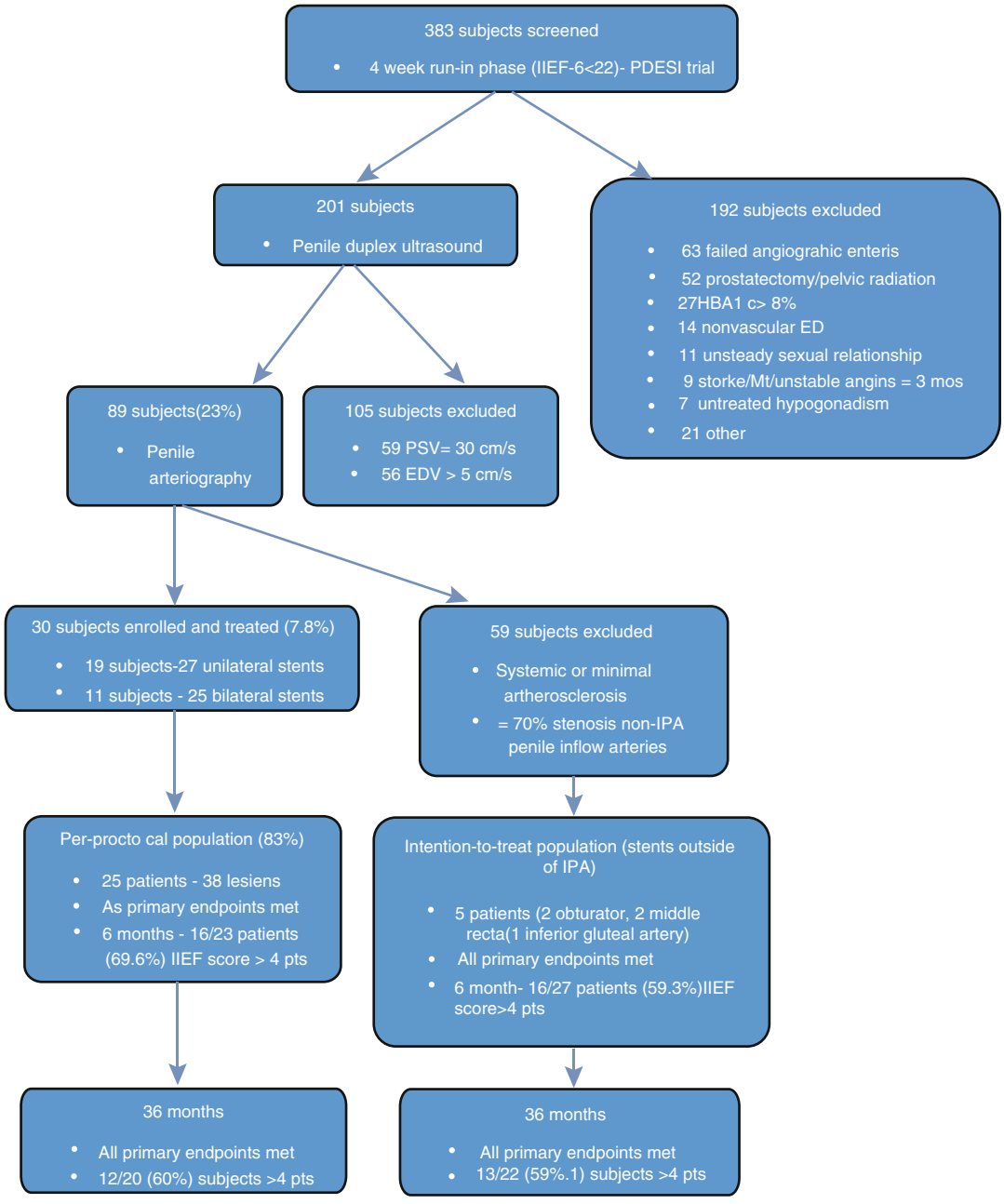

Fig. 16.5 ZEN trial flow chart

Primary endpoints included safety at 30 days and feasibility at 30 days. Safety was defined as major adverse events including device or procedure-related death, perineal gangrene or necrosis, or need for perineal/penile/anal surgery. Feasibility was defined as improvement in IIEF-6 scores greater than 4 points in 50 % of treated patients. Forty-five lesions in the 30 patients were treated with 100 % technical success with no major adverse events up to 6 months follow-up. Mean IIEF-6 scores were 15.5 ± 4.2 pre-procedure, 22.4 ± 6.3 at 3 months, and 21.8 ± 6.5 at 6 months. Meaningful improvement in IIEF score (59.3 %) was observed at 3 and 6 months, and thus both safety and feasibility endpoints were met. This subjective improvement correlates with nonsignificant increases in PSV observed via evaluable penile duplex ultrasound of the stented IPAs with mean peak systolic velocities seen of 16.4 ± 8.1 cm/s at baseline, 28.8 ± 10.0 cm/s at 1 month, 42.0 ± 26.0 cm/s at 6 months, and 32.4 ± 10.1 cm/s at 1-year follow-up. A significantly increased rate of restenosis was observed in 11/32 lesions (34.4 %) at 6 months, when compared with the 9.2 % restenosis rate for DES in the coronary vasculature, with no relationship observed with IIEF-6 scores in clinical follow-up [70]. This could be due to predominant low flow conditions during flaccid states in pudendal arteries where episodic suprasystolic pressures and high flow are only observed in a very limited capacity during erections, opposed to coronary arteries that experience more constant high flow rates. The high restenosis rate may also highlight that like coronary stenting for CAD, pudendal stenting for ED requires concomitant, adjuvant medical therapy and lifestyle changes for their optimization. Restenosis rates are discussed further in the next section of this chapter.

The ZEN trial has been the only penile arterial revascularization study to have a standardized definition of ED and the only study to exclude veno-occlusive disease which has been shown to occur in up to 47 % of patients [44]. Thus, pudendal artery stent placement for the treatment of vasculogenic ED will not offset the pool of candidates for inflatable penile prostheses, as it is not indicated for patients with venous leak.

Limitations for the ZEN trial include a small sample size and incomplete follow-up, which makes definitive conclusions difficult to establish. The trial was limited by a lack of a control arm and high screening failure rate with only 7.8 % subjects screened being enrolled in the trial, highlighting the need for appropriate patient selection with pre-procedural diagnostic imaging including improved noninvasive angiographic screening modalities to directly link pelvic arterial disease with ED. However, this figure is consistent with the frequency of isolated IPA lesions identified in patients with ED observed in multiple imaging modalities in several studies [52, 71, 72]. In addition, 5 of the 30 patients (16 %) had non-IPA vessels stented without major adverse events, and 3 of 30 patients (10 %) were lost to follow-up. This emphasizes the considerable learning curve facing interventionalists, as several stents were placed outside of the pudendal arteries due to the degree of anatomic variation. The Incidence of Male Pudendal Artery Stenosis in Suboptimal Erections Study (IMPASSE) was a multicenter trial designed by the ZEN investigators that aimed to improve patient selection by defining normal pelvic arterial anatomy and correlating observed vasculogenic lesions for ED with coronary pathology in men scheduled to undergo heart catheterization. The trial intended to enroll 350 male patients between 35 and 70 years old undergoing angiography for CAD or PAD with follow-up at 1, 2, and 3 years. However, the trial was suspended due to budgetary constraints. Again, this underscores the need for further angiographic trials to describe pelvic arterial anatomy for the progression of endovascular repair of internal pudendal artery stenoses in the treatment of vasculogenic ED.

To improve patient selection, a trial including patients already managed on dual antiplatelet therapy of aspirin and clopidogrel with their history of CAD would confer no additional pharmacotherapeutic risk with IPA DES stents [73]. Patients on nitrates should also be included, with the established correlation of CAD and ED as extensions of a macrovascular, systemic, atherogenic process. These patient criteria excluded a significant proportion of the population from the ZEN trial that may benefit from such endo-

vascular therapy. A different route for a study could focus on ED in young males secondary to blunt pelvic trauma from focal arterial lesions as many historical pelvic revascularization studies have focused upon [73]. This may improve patient selection by focusing on patients with focal lesions, rather than a diffuse macrovascular atherosclerotic process.

Pudendal Artery Stent Restenosis

The ZEN trial observed much higher restenosis rates at 6 months (34 %) than has been observed in coronary circulation (9.2 %). This large variance highlights unknowns in applying drug-eluting stents (DES) to the pelvic vasculature [23]. Since coronary artery restenosis has been researched more extensively than pudendal artery restenosis, it is feasible to examine coronary artery restenosis in hopes of applying these principles to pudendal artery stents.

Restenosis is defined as diameter stenosis ≥50 % of the in-segment area. This includes the stent area and 5 mm segments proximal and distal to the stent edges [74]. Causes of restenosis can be attributed to many etiologies. One of the major contributors of restenosis is underexpansion of the stent. Underexpansion can be caused by low deployment pressures or undersizing of the stent within the vasculature [75]. Conversely, the presence of heavily calcified lesions may cause resistant stent under expansion even in the presence of adequate or high dilation pressures [76]. It is possible to have restenosis even with sufficiently expanded stents. Stent misplacement or stents that do not fully cover an underlying lesion can cause the appearance of restenosis. This causes a "candy wrapper" angiographic appearance and is usually found in patients treated with DES or brachytherapy [75]. There is a sharp contrast between the stent lumen and focal edge restenosis in this unique angiographic finding. The restenosis could represent negative vasculature remodeling, plaque growth, or both. Another cause of restenosis is stent fracture. Fracture can potentially lead to stent thrombosis and is more often seen in some DES types and within certain vessels such as the right coronary artery. Lastly, with the recent introduction of DES, drug resistance and local hypersensitivity reactions have been noted causes for restenosis [75].

Understanding restenosis rates of different stent types in coronary arteries can help guide stent selection for penile arterial revascularization. Bare metal stents (BMS) were utilized from 1998 to 2002 and were shown to have a 30.1 % restenosis rate [74]. Subsequently, first-generation DES therapy was made available which comprised of sirolimus-eluting stents, polymer-based paclitaxel-eluting stents, and phosphorylcholine polymer-based zotarolimus-eluting stents. They exhibited a 14.6 % restenosis rate [74]. DES therapy was a substantial milestone in coronary intervention due to the significantly lower restenosis rates compared with BMS. In January 2006, second-generation drug-eluting stents were introduced which were comprised of polymer-based everolimus-eluting stents, biolynx polymer-based zotarolimus-eluting stents, biodegradable polymer-based sirolimus-eluting stents, and sirolimus- and probucol-eluting stents. These second-generation DES demonstrated a 12.2 % restenosis rate. Thus, it can be concluded that intervention with a second-generation DES demonstrates better antistenotic efficacy in comparison with first-generation DES and BMS [74].

Initial studies revealed that the strongest predictors for BMS restenosis were small vessel size, increased lesion and stent length, and the presence of diabetes mellitus [74]. Predictors for DES restenosis had not been known until as of recent when more studies were made available. The strongest predictors for DES restenosis were found to be small vessel size, increased stent length, final percentage of diameter stenosis, diabetes mellitus, differential anti-restenotic potency of DES, in-stent restenosis, and ostial lesion location [74]. Overall, regardless of the stent being used, small vessel size and increased length of segment stented were the strongest predictors of restenosis.

Recent investigations have helped guide new practices to implement in prevention of restenosis

in coronary arteries. Antiplatelet drug therapy for 6–12-month duration has been recommended in patients who are treated with DES for restenosis. Abciximab and oral sirolimus have been used in the past in patients with coronary restenosis; however, later trials have failed to demonstrate clinical benefit from this additional therapy. In addition, oral sirolimus has demonstrated a higher incidence of adverse drug effects [75].

Other efforts to reduce restenosis rates have focused on stenting procedures. It has been shown that direct stenting without predilation was a safe and effective treatment modality in treating percutaneous coronary intervention [76]. This practice to reduce the risk of restenosis is an extrapolation of previous data that showed that direct stenting may reduce the degree of intimal hyperplasia compared with previous balloon dilation [3]. Furthermore, predilation may induce dissection necessitating longer stents that may increase restenosis. The direct Stenting to Reduce Restenosis in Stent Era with Drug Elution (STRESSED) study did not find a difference in restenosis rates between direct DES implantation compared with conventional DES implantation [76]. However, the study did find a higher restenosis rate in provisional stenting with DES [76].

Repeat stenting with DES has been shown to be an effective and safe treatment for in-stent restenosis. There has been ongoing debate on whether the implantation of the same type of DES (homogenous or homo-DES) or implantation of a different type of DES (heterogeneous or hetero-DES) is more effective in reducing restenosis rates. The rationale behind the hetero-DES is based on the hypothesis that the different DES will elute a drug that will overcome drug resistance of specific polymer-related problems [77]. Currently, results remain inconclusive, and the evidence favoring implementation of hetero-DES is weak [75, 77]. Although there are no clear benefits from a switch DES strategy, some studies have shown that the hetero-DES approach was associated with better clinical outcomes [75]. Plain balloon angioplasty and drug-coated balloon angioplasty are other viable treatment options for DES in-stent restenosis. Plain balloon angioplasty has demonstrated high restenosis rates of 40 % or more [77]. Subsequently, drug-coated balloons (DCB) were developed and have consistently shown to significantly reduce restenosis rates when compared to plain balloon angioplasty. Recent investigations have also demonstrated that DCB have similar restenosis rates to first-generation DES in patients with BMS or DES restenosis [75]. In summary, DCB or repeat DES implantation, either homo-DES or hetero-DES, is superior to plain balloon angioplasty for preventing recurrent restenosis [75, 77].

Pelvic Arterial Imaging Modalities

A comprehensive understanding of the male pelvic arterial system is paramount to help guide vasculogenic erectile dysfunction diagnosis and treatment. Due to the complexity and variability of the male pelvic arterial system, the branches of the internal iliac artery may be difficult to identify and differentiate. Most commonly, the IPA originates from the anterior division of the internal iliac artery in 63 % of cases [78]. The next most common origin of the IPA was the gluteopudendal trunk (19 %) and then lastly from accessory vessels (18 %) [6]. This large variability presents a significant challenge to characterize pelvic arterial vasculature. The rapidly growing interest in endovascular treatment of vasculogenic erectile dysfunction warrants the need to find pudendal lesions more efficiently.

Currently in penile revascularization studies, pulsed wave color duplex ultrasound is used as a first-line diagnostic screening tool, able to detect lesions from the proximal iliac to distal cavernosal arteries, as well as veno-occlusive lesions through measuring PSV, end diastolic velocity, resistive index, acceleration time, and degree of arterial dilation [79]. A PSV <25 cm/s within 5 min of ICI has a sensitivity of 100 % and specificity of 95 % for patients with PAI on angiography, while an EDV of >5 cm/s demonstrates veno-occlusive dysfunction [80, 81]. It is radiation-free, cost-effective, and mainly used as an ED screening test by assessing the arterial inflow and venous outflow. However, the gold

standard for diagnosis of vasculogenic ED remains invasive angiography in combination with intracavernosal injection which is able to illustrate the pelvic and penile vasculature with its collaterals and anatomic variations. Duplex ultrasound can be combined with intracavernosal injection with vasoactive agents to assess patients with significant clinical suspicion for vasculogenic erectile dysfunction [82]. However, duplexes are unable to provide information proximal to the cavernosal artery concerning topography or pathology of the ilio-pudendal-penile arterial system [83]. Furthermore, duplex ultrasound is highly operator dependent, incurring incorrect diagnoses due to anatomical variation, lack of standardization in vasoactive agents, and procedure-related anxiety causing suboptimal erections during the exam [84]. One study has even questioned the ability of duplex ultrasounds to accurately diagnose venous leaks, despite previous data establishing its value in assessing arterial inflow and venous outflow [82]. The most valuable parameters in diagnosing vasculogenic erectile dysfunction are still a topic of debate. Peak systolic flow velocity, end diastolic velocity, resistive index, acceleration time, and degree of arterial dilation of the cavernosal arteries have all been shown as viable measurements in evaluating erectile dysfunction [82]. Subjects in the ZEN trial were selected via duplex ultrasound and eligibility assessed on cavernosal artery diameters as well as peak systolic velocity. End diastolic velocities were also assessed at peak erection with venous leak defined as >5 cm/s [23].

Dynamic infusion cavernosometry and cavernosography (DICC) is another way that has been validated to evaluate arterial and venous insufficiency leading to ED. Cavernosometry involves intracavernous injection of a vasodilator followed by contrast infusion while monitoring intracavernosal pressures to assess the penile outflow system. Contrast is infused until a pressure of 150 mmHg is reached, whereupon pressure decrements are trended for 30 s. Veno-occlusive dysfunction is indicated by either an inability to increase intracavernous pressure to the level of systolic blood pressure or a rapid decrease in pressure after stopping the infusion. Brachial pressure is also monitored to calculate a brachial-cavernosal gradient. A gradient higher than 35 mmHg is indicative of arterial insufficiency. Cavernosal artery systolic occlusion pressures obtained during DICC have been reported to correlate well with arteriography [77]. To visualize any sites of venous leak, anteroposterior and oblique images are acquired once an artificial erection is maintained to better localize the defect.

Virtual cavernoscopy is an emerging technique that shows promise in visualizing the corpus cavernosum in patients with ED. The modality facilitates perception of the internal surface and structures of the corpus cavernosum such as the septum and cavernous artery, as well as assessment of venous outflow [85]. There has only been one study thus far which has examined this imaging modality, and the initial results are encouraging. Virtual cavernoscopy involves reconstructing images using cross-sectional CT data to create three-dimensional images of the corpus cavernosum. Images are acquired as contrast medium fills the corpus cavernosum, while no contrast fills the artery. Since this allows for visualization of the artery as the reversed image of the filling defect, blood flow would not affect the quality of visualizing the artery unlike other methods such as CT angiography and Doppler which struggle to visualize arteries with decreased or no blood flow [85]. In the study by Izumi et al., 50 of 80 cavernosal arteries were detected by virtual cavernoscopy that were undetected by CT angiography [85]. Virtual cavernoscopy can also assess venous leakages. Since the corpus cavernosum is visualized from the inside via virtual cavernoscopy, it can show the origin of the venous outflow system with increased accuracy compared to cavernosography in certain situations such as excessive venous outflow. However, there remain technical difficulties and limits for this imaging modality as the adequacy of the image depends on the filling of the corpus cavernosum with sufficient contrast medium. Izumi et al. reported 16 of 80 cases in which they were unable to acquire an adequate image due to insufficient contrast filling in the corpus cavernosum.

Thus, improved filling methods and further refinements to this technique are needed for it to prove reliably practical in a clinical setting [85].

While duplex ultrasound is the primary screening tool for vasculogenic erectile dysfunction, intra-arterial digital subtraction angiography (DSA) is considered the gold standard for consideration of penile arterial revascularization. It was used in the ZEN trial to define the anatomic features of all erectile-related arteries [23]. Intra-arterial DSA has the ability to accurately depict the pelvic and penile vasculature anatomic variations, steno-occlusive disease, and collateral networks [82]. Its images offer the best detail of the terminal branches of the internal pudendal artery, especially when there is extensive calcification [78, 84]. There are some disadvantages to DSA. The procedure is expensive and semi-invasive, requires a larger amount of contrast medium compared with CT angiography, and requires a longer examination time [84]. Other complications of DSA include arteriovenous fistula, pseudoaneurysm formation, infection, dissection, local hematoma, allergic reactions, and sensation of pain or heat in the gluteal, perineal, and genital areas [82]. S. Spiliopoulos et al. outline indications for intra-arterial DSA: patients with inflow arterial disease and outflow venous disease who are candidates for treatment with endovascular treatment, the confirmation of organic causes of ED (even if no treatment is available to give patients psychological relief), and confirmation of vasculogenic post-traumatic ED [82].

Other noninvasive imaging modalities have emerged to assess the penile vascular supply in patients with suspected vasculogenic ED. Three-dimensional multidetector computed tomography (MDCT) with contrast has been proven to be valuable and allows for a noninvasive imaging modality to adequately visualize the penile arterial system. No image manipulation is necessary allowing for more rapid acquisition. There are some disadvantages to MDCT as well: MDCT has higher radiation doses and uses more contrast compared with other imaging modalities. The accuracy of MDCT has also been shown to be limited by the presence of extensive calcification around the vessels. In such cases, DSA is the best modality in assessing internal pudendal artery patency [78]. Previous studies assessing the diagnostic accuracy of CT angiography have shown that compared to DSA, CTA had troubles clearly delineating the anatomic features of smaller arteries of the penis such as the common penile artery [83, 84]. Some of the difficulties evaluating the cavernosal arteries were attributed to the overlay of the cavernosal arteries in the cavernosal bodies. Comparing MDCT to DSA in assessing the proximal IPA, MDCT had a high false-positive rate and a low false-negative rate. In assessing the distal IPA, MDCT showed a high sensitivity and low specificity [78]. Wang et al. [83] recently assessed in the Pelvic Revascularization For arteriogenic EreCTile dysfunction (PERFECT-1) study the feasibility of CTA as a noninvasive diagnostic tool for patients with ED to improve overall patient selection in vasculogenic ED trials. Previous CTA reports were only able to visualize the arterial architecture to the level of the IPA but not the common penile artery [78]. The Wang study utilized a sliding-thin-slab maximum intensity projection reformation technique and MDCT with a 64-detector row CT scanner that extended this imaging modality's diagnostic capability to visualize vessels with a diameter of 1 mm or less, such as the dorsal penile artery and proximal cavernosal artery (Fig. 16.6a, b) [83]. However, only 20 of 120 patients screened (15 %) were enrolled in this trial again highlighting the need for an improvement in patient selection extending beyond bettering screening imaging modalities.

Three-dimensional magnetic resonance angiography has the ability to accurately evaluate iliac, pudendal, perineal, and common penile arteries for vasculogenic ED with dynamic gadolinium enhancement. The characterization of smaller end arteries of the penis has not been reliably demonstrated with MR angiography [86]. Direct head-to-head studies have revealed that DSA is superior in evaluation of the penile vascular system especially in characterizing distal penile arteries [87].

As previously stated, the male pelvic arterial system is very complex and extremely variable

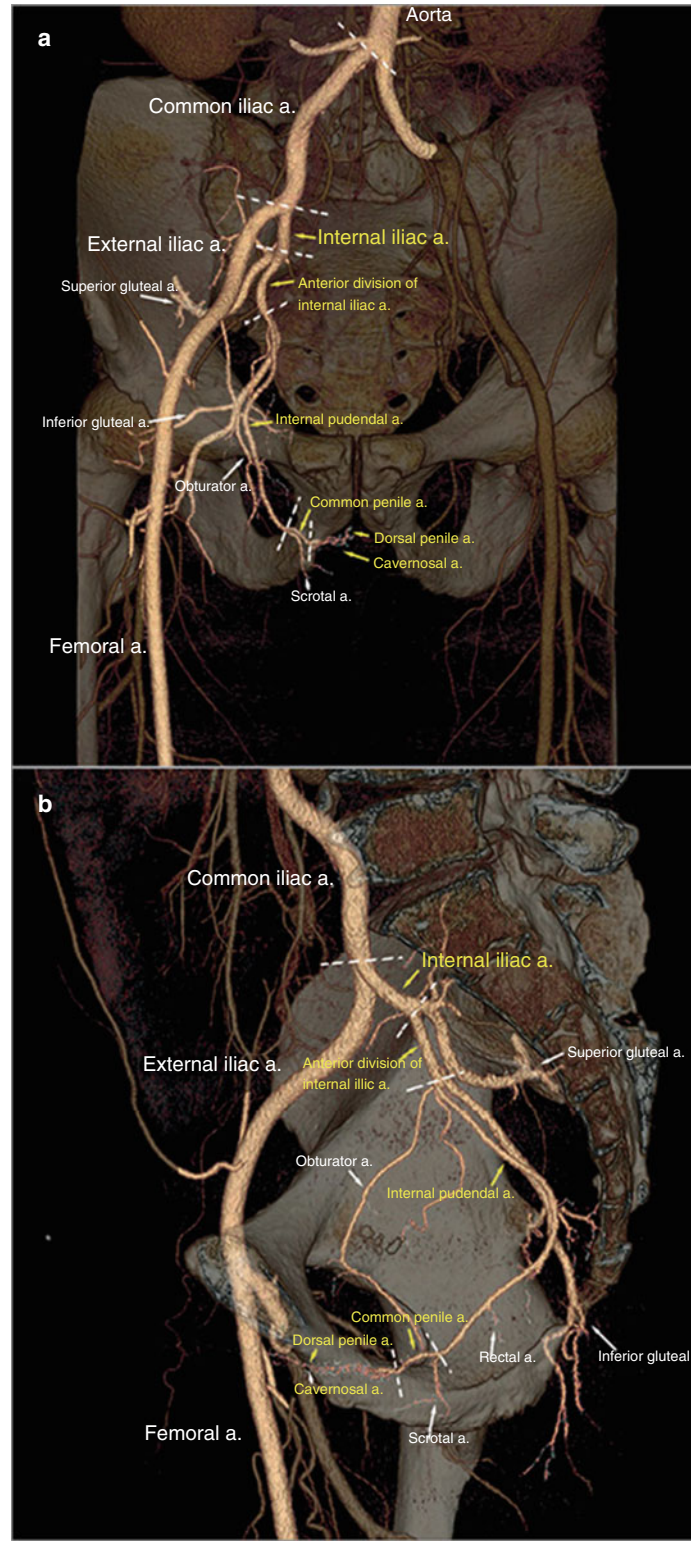

Fig. 16.6 (**a**, **b**) Pelvic CT angiography of pelvic arterial anatomy. (**a**) 3D volume-rendered (VR) anterior reconstruction of the right-sided pelvic arteries (Erectile related, yellow; non-erectile related, white). (**b**) 3D VR oblique lateral reconstruction of the right-sided pelvic arteries (Used from Wang TD, et al. Safety and 6-month durability of angioplasty for isolated penile artery stenoses in patients with erectile dysfunction: a first-in-man study. EuroIntervention 2014; 10(1):147–156. With permission from Europa Digital & Publishing)

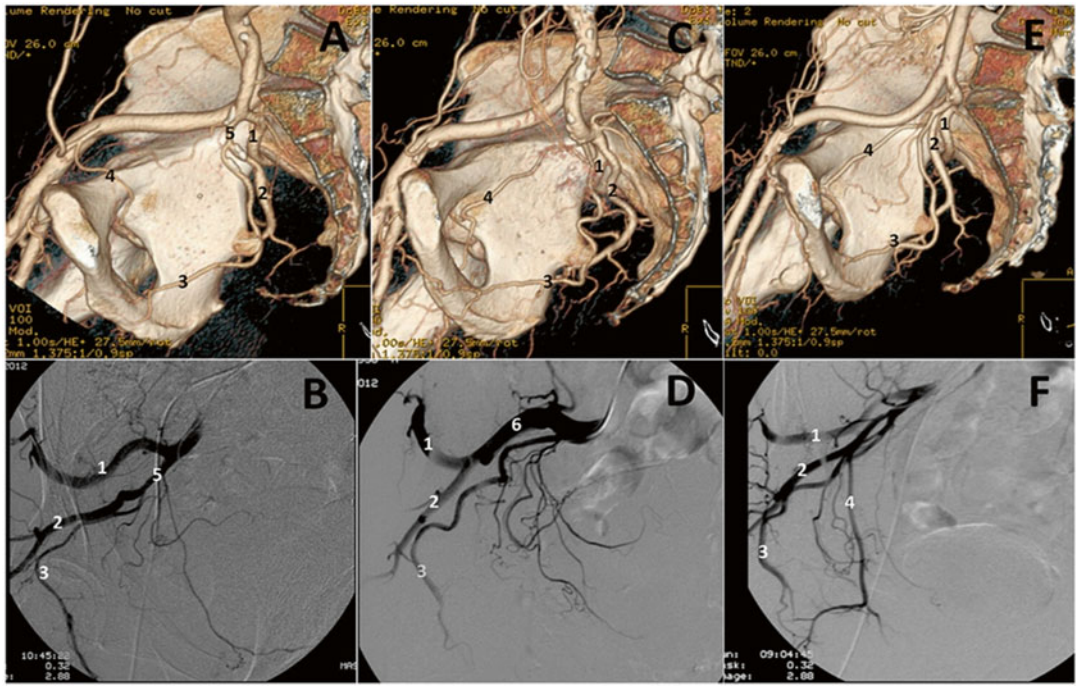

Fig. 16.7 (**a**–**f**) Internal iliac branching patterns. (**a**) CTA 3D reconstruction. (**b**) Selective DSA of right internal iliac artery showing a group A branching pattern. Note that the internal pudendal and the inferior gluteal arteries have a common origin on the gluteo-pudendal trunk [5]. (**c**) CTA 3D reconstruction. (**d**) Selective DSA of right internal iliac artery showing a group B branching pattern. Note the posterior division common gluteal trunk [6] that originates the superior and inferior gluteal arteries. (**e**) CTA 3D reconstruction. (**f**) Selective DSA of right internal iliac artery showing a group C branching pattern. Note the three main collaterals arise from the internal iliac artery at a common origin. Also note the variable origins of the obturator artery [4], arising from the inferior epigastric artery (**a**, **b**) or the internal iliac artery collaterals (**c**, **e**, **f**) (1. superior gluteal artery, 2. inferior gluteal artery, 3. internal pudendal artery, 4. obturator artery, 5. common gluteo-pudendal trunk, 6. common gluteal trunk) (Used with permission from Pereira JA, et al. Radiologic anatomy of arteriogenic erectile dysfunction: a systematized approach. Acta Med Port 2013; 26(3):219–225)

with the IPA not always being readily identifiable. The Yamaki classification system, which is based on the branching points of the main collaterals of the internal iliac artery, has been suggested to be a viable approach to characterize the arteries of the male pelvis [88]. Using the Yamaki classification, the internal iliac arteries are classified into four groups (Fig. 16.7a–f).

In group A, the internal iliac artery divides into two major branches, the superior gluteal artery and the common trunk of the inferior gluteal and internal pudendal artery. Group B defines the internal iliac artery dividing into the internal pudendal artery and common trunk of the superior gluteal and inferior gluteal arteries. In group C, all three main internal iliac branches have independent origins simultaneously. Group D classifies the superior gluteal and internal pudendal artery having the same origin and the inferior gluteal artery originating independently (not pictured) [88]. The Yamaki classification does not take into account the obturator artery due to its highly variable origins within and outside of the pelvic arterial system [89]. This schema can be applied within multiple imaging modalities such as MR angiography, CTA, and DSA. It allows for easy, reproducible recognition of the main collaterals of the internal iliac artery. Furthermore, it has been shown to be effective even in the presence of diffuse atherosclerotic changes in the vessels during vasculogenic ED [84].

Transluminal Balloon Angioplasty for Penile Arterial Revascularization

Current work on treating vasculogenic erectile dysfunction with transluminal angioplasty is very limited. There have been nine studies overall and only two have been conducted within the past 5 years (ZEN and PERFECT-1) [21]. Furthermore, most of the studies focus on large-vessel inflow disease such as the common, external, and internal iliac arteries; only two studies including the ZEN trial examined the internal pudendal arteries and the PERFECT-1 study which examined more distal arteries (Table 16.2) [21]. The PERFECT-1 study was a 6-month trial for balloon angioplasty of isolated IPA lesions: the first in-man study to assess the safety and efficacy of balloon angioplasty for isolated penile artery stenoses in patients with vasculogenic erectile dysfunction. The study used multidetector CT angiography with nitroglycerine to visualize the penile arterial system. After assessing which arteries had stenotic lesions, a 5 Fr guiding catheter was used to engage the internal pudendal artery followed by treating the lesion with a .014 in. steerable guide wire that was advanced across the stenosis. A 1.0 mm diameter balloon catheter was initially used and then advanced in size until the balloon catheter size was approximately equal to the reference vessel diameter. Overall, 20 patients met the inclusion criteria and underwent successful invasive angioplasty in 23 vessels [83]. Clinical success was defined as a change of IIEF-5 score improvement of ≥4 and was achieved in 75, 65, and 60 % of patients at 1, 3, and 6 months, respectively. The 60 % success rate is very similar to what was found in the ZEN trial where 59.3 % of patients with erectile dysfunction displayed an improvement in IIEF-5 scores ≥4 at 6-month follow-up after internal pudendal artery stenting. And the restenosis rate of 45 % (9/20) was slightly higher than that exhibited by the ZEN trial (34 %) at 6 months. However, follow-up MDCT was scheduled at 6–9 months after angioplasty and was not included in the study, which may facilitate elucidation of responsiveness to therapy and restenosis rates. The study also demonstrated the capability of interventionalists to start with a small balloon catheter (1 mm) and progressively upsize balloon catheters to match reference vessel size in order to prevent dissection [83]. Overall, the PERFECT-1 study demonstrated that balloon angioplasty in penile artery lesions

Table 16.2 Endovascular penile arterial revascularization studies

Study	*n*	Angiographic stenosis	Technique	Follow-up	Success rate
Casaneda-Zunga [46]	2	Internal iliac	PTA	18 months	2/2 (100 %)
Van Unnik [47]	1	External iliac	PTA	N/A	1/1 (100 %)
Goldwasser [49]	1	Internal iliac	N/A	N/A	1/1 (100 %)
Dewar [48]	30	70 % aortoiliac 40 % internal iliac	PTA	N/A	10/33 (33 %)
Angelini [50]	5	100 % internal iliac	PTA	2–18 months	4/5 (80 %)
Valji [44]	3	N/A	PTA	N/A	N/A
Urigo [21, 51][a]	23	65 % internal iliac 13 % internal pudendal	N/A	N/A	15/23 (65 %) 3/3 (100 %)
Rogers [23]	30	100 % internal pudendal	DES	6 months	59.3 % had improvement in IIEF score >4 points
Wang [83]	20	100 % penile	PTA	6 months	60 % had improvement in IIEF score >4 points

IIEF international index on erectile function, *PTA* percutaneous transluminal angioplasty, *DES* drug-eluting stents, *N/A* not available

Adapted with permission from Philip F, Shishehbor MH. Current state of endovascular treatment for vasculogenic erectile dysfunction. Curr Cardiol Rep 2013;15(5): 360

[a]65 % of patient with internal iliac artery stenosis had improvement in erectile function, 100 % with pudendal artery stenosis

is safe and can achieve clinically significant improvement in vasculogenic erectile dysfunction. The small study size and short duration of follow-up still warrants further confirmatory investigation. It can be speculated from the conclusions of the ZEN trial and PERFECT-1 study that when the distal arteries are revascularized, the rate-limiting flow can still be from the more proximal IPA. Conversely, if the IPA is solely stented, distal arteries may still contain stenotic lesions that prohibit adequate blood flow. Thus, a combination of stent placement in the IPA and balloon angiography in the more distal vasculature may lead to increased blood flow and therefore increased erection quality.

References

1. NIH Consensus Conference. Impotence: NIH consensus development panel on impotence. JAMA. 1993;270(1):83–90.
2. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180–9.
3. Ayta IA, McKinlay JB, Krane RJ, et al. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int. 1999;84(1):50–6.
4. Smith KJ, Roberts MS. The cost-effectiveness of sildenafil. Ann Intern Med. 2000;132(12):933–7.
5. Willke RJ, Yen W, Yang SC, et al. Quality of life effects of alprostadil therapy for erectile dysfunction: results of a trial in Europe and South Africa. Int J Impot Res. 1998;10(4):239–46.
6. Campbell HE. Clinical monograph for drug formulary review: erectile dysfunction agents. J Manag Care Pharm. 2005;11(2):151–71.
7. Montague DK, Jarow JP, Broderick GA, et al. Chapter 1: the management of erectile dysfunction: an AUA update. J Urol. 2005;174(1):230–9.
8. Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. JAMA. 2005;294(23):2996–3002.
9. El-Sakka AI, Morsy AM, Fagih BI, et al. Coronary artery risk factors in patients with erectile dysfunction. J Urol. 2004;172(1):251–4.
10. Rosen MP, Greenfield AJ, Walker TG, et al. Cigarette smoking: an independent risk factor for atherosclerosis in the hypogastric-cavernous arterial bed of men with arteriogenic impotence. J Urol. 1991;145(4):759–63.
11. Gazzaruso C, Giordanetti S, De Amici E, et al. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. Circulation. 2004;110(1):22–6.
12. Chiurlia E, D'Amico R, Ratti C, et al. Subclinical coronary artery atherosclerosis in patients with erectile dysfunction. J Am Coll Cardiol. 2005; 46(8):1503–6.
13. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol. 2011;58(13):1378–85.
14. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol. 2003;44(3):360–4. discussion 364–365.
15. Bookstein JJ, Valji K, Parsons L, et al. Pharmacoarteriography in the evaluation of impotence. J Urol. 1987;137(2):333–7.
16. Mueller SC, von Wallenberg-Pachaly H, Voges GE, et al. Comparison of selective internal iliac pharmacoangiography, penile brachial index and duplex sonography with pulsed Doppler analysis for the evaluation of vasculogenic (arteriogenic) impotence. J Urol. 1990;143(5):928–32.
17. Rosen MP, Greenfield AJ, Walker TG, et al. Arteriogenic impotence: findings in 195 impotent men examined with selective internal pudendal angiography. Young Investigator's Award. Radiology. 1990;174(3 Pt 2):1043–8.
18. Kloner RA, Mullin SH, Shook T, et al. Erectile dysfunction in the cardiac patient: how common and should we treat? J Urol. 2003;170(2 Pt 2):S46–50. discussion S50.
19. Montorsi F, Salonia A, Deho F, et al. Pharmacological management of erectile dysfunction. BJU Int. 2003;91(5):446–54.
20. Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. Lancet. 1985;1(8422):181–4.
21. Philip F, Shishehbor MH. Current state of endovascular treatment for vasculogenic erectile dysfunction. Curr Cardiol Rep. 2013;15(5):360.
22. Rogers JH, Rocha-Singh KJ. Endovascular therapy for vasculogenic erectile dysfunction. Curr Treat Options Cardiovasc Med. 2012;14(2):193–202.
23. Rogers JH, Goldstein I, Kandzari DE. Zotarolimus-eluting peripheral stents for the treatment of erectile dysfunction in subjects with suboptimal response to phosphodiesterase-5 inhibitors. J Am Coll Cardiol. 2012;60(25):2618–27.
24. Kinsey AC, Pomeroy WR, Martin CE, et al. Sexual behavior in the human male. Am J Public Health. 2003;93(6):894–8.
25. Saenz de Tejada I, Goldstein I, Azadzoi K, et al. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med. 1989;320(16): 1025–30.

26. Rajfer J, Rosciszewski A, Mehringer M. Prevalence of corporeal venous leakage in impotent men. J Urol. 1988;140(1):69–71.
27. Metz P, Ebbehoj J, Uhrenholdt A, et al. Peyronie's disease and erectile failure. J Urol. 1983;130(6): 1103–4.
28. Dalkin BL, Carter MF. Venogenic impotence following dermal graft repair for Peyronie's disease. J Urol. 1999;46(3):849–51.
29. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am. 2005;32(4):379–95. v.
30. Greenstein A, Chen J, Miller H, et al. Does severity of ischemic coronary disease correlate with erectile function? Int J Impot Res. 1993;9(3):123–6.
31. Montorsi P, Ravagnani PM, Galli S, et al. The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. Am J Cardiol. 2005;96(12B):19M–23.
32. Gandaglia G, Briganti A, Montorsi F, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65:968–78. Eur Urol 66(5): e88–89.
33. Azadzoi KM, Goldstein I, Siroky MB, et al. Mechanisms of ischemia-induced cavernosal smooth muscle relaxation impairment in a rabbit model of vasculogenic erectile dysfunction. J Urol. 1998;160(6 Pt 1):2216–22.
34. Azadzoi KM. Vasculogenic erectile dysfunction: beyond the haemodynamic changes. BJU Int. 2006;97(1):11–6.
35. Lue TF. Erectile dysfunction. N Engl J Med. 2000;342(24):1802–13.
36. Siroky MB, Azadzoi KM. Vasculogenic erectile dysfunction: newer therapeutic strategies. J Urol. 2003;170(2 Pt 2):S24–9. discussion S29–30.
37. Leriche R. Des obliterations arterielle hautes (oblideration de la termination de l'aorte) comme cause de insufficances circulatoire des membres inferieurs (abstr). Bull Mem Soc Chir. 1923;49:1404.
38. May AG, Deweese JA, Rob CG. Changes in sexual function following operation on the abdominal aorta. Surgery. 1969;65(1):41–7.
39. Carstensen G. Treatment of impotentia coeundi by reconstructing the circulation in the internal iliac artery. Langenbecks Arch Chir. 1969;325:885–8.
40. Michal V, Kramar R, Pospichal J, et al. Direct arterial anastomosis on corpora cavernosa penis in the therapy of erective impotence. Rozhl Chir. 1973;52(9):587–90.
41. Zorgniotti AW, Padula G, Rossi G. Impotence caused by pudendal arteriovenous fistula. Urology. 1979; 14(2):161–2.
42. Ginestie J, Romieu A. The treatment of impotence of vascular origin. Revascularisation of the corpora cavernosa. J Urol Nephrol. 1976;82(10-11):853–9.
43. Michal V, Pospischal J. Phalloarteriography in the diagnosis of erectile impotence. World J Surg. 1978;2(2):239–48.
44. Valji K, Bookstein JJ. Transluminal angioplasty in the treatment of arteriogenic impotence. Cardiovasc Intervent Radiol. 1988;11(4):245–52.
45. Shishehbor MH, Philip F. Endovascular treatment for erectile dysfunction: an old paradigm revisited. J Am Coll Cardiol. 2012;60(25):2628–30.
46. Castaneda-Zuniga WR, Gomes A, Weens C, et al. Transluminal angioplasty in the management of mesenteric angina. Rofo. 1982;137(3):330–2.
47. Van Unnik JG, Marsman JW. Impotence due to the external iliac steal syndrome treated by percutaneous transluminal angioplasty. J Urol. 1984;131(3):544–5.
48. Dewar ML, Blundell PE, Lidstone D, et al. Effects of abdominal aneurysmectomy, aortoiliac bypass grafting and angioplasty on male sexual potency: a prospective study. Can J Surg. 1985;28(2):154–6. 159.
49. Goldwasser B, Carson CC, Braun SD, et al. Impotence due to the pelvic steal syndrome: treatment by iliac transluminal angioplasty. J Urol. 1985;133(5):860–1.
50. Angelini G, Pezzini F, Mucci P. Arteriosclerosis and impotence. Minerva Psichiatr. 1985;26(4):317–53.
51. Urigo F, Pischedda A, Maiore M, et al. Role of arteriography and percutaneous transluminal angioplasty in the diagnosis and treatment of arterial vasculogenic impotence. Radiol Med. 1994;88(1–2):86–92.
52. Wang TD, Lee WJ, Chen WJ, et al. Comprehensive assessment of prevalence and distribution of obstructive pelvic arterial lesions by computed tomography angiography in patients with erectile dysfunction. J Am Coll Cardiol. 2013;62:B160.
53. Rogers JH, Karimi H, Kao J. Internal pudendal artery stenoses and erectile dysfunction: correlation with angiographic coronary artery disease. Catheter Cardiovasc Interv. 2010;76(6):882–7.
54. Jarow JP, DeFranzo AJ. Long-term results of arterial bypass surgery for impotence secondary to segmental vascular disease. J Urol. 1996;156(3):982–5.
55. Simonsen U, Garcia-Sacristan A, Prieto D, et al. Penile arteries and erection. J Vasc Res. 2003; 39(4):283–303.
56. Prieto D. Physiological regulation of penile arteries and veins. Int J Impot Res. 2008;20(1):17–29.
57. Anderson KE. Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. Pharmacol Rev. 1993;45(3):253–308.
58. Andersson KE, Wagner G. Physiology of penile erection. Physiol Rev. 1995;75(1):191–236.
59. Manabe K, Heaton JP, Morales A, et al. Pre-penile arteries are dominant in the regulation of penile vascular resistance in the rat. Int J Impot Res. 2000; 12(3):183–9.
60. Zweifach BW, Lipowsky HH. Pressure-flow relations in blood and lymph microcirculation. In: Handbook of physiology, Section 2: the cardiovascular system, vol. 4, microcirculation Part 1, Chapter 7. Bethesda, MD: American Physiological Society; 1984. p. 231–307.
61. Hannan JL, Blaser MC, Oldfield L, et al. Morphological and functional evidence for the contribution of the pudendal artery in aging-induced erectile dysfunction. J Sex Med. 2010;7(10):3373–84.
62. Hannan JL, Blaser MC, Oldfield L, et al. Impact of hypertension, aging, and antihypertensive treatment on the morphology of the pudendal artery. J Sex Med. 2011;8(4):1027–38.

63. Folko B. Physiological aspects of primary hypertension. Physiol Rev. 1982;62(2):347–504.
64. Huguet JF, Clerissi J, Juhan C. Radiologic anatomy of pudendal artery. Eur J Radiol. 1981;1(4):278–84.
65. Bahren W, Gall H, Scherb W, et al. Arterial anatomy and arteriographic diagnosis of arteriogenic impotence. Cardiovasc Intervent Radiol. 1988;11(4): 195–210.
66. Bruhlmann W, Pouliadis G, Zollikofer C, et al. Arteriography of the penis in secondary impotence. Urol Radiol. 1982;4(4):243–9.
67. Buvat J, Lemaire A, Besson P, et al. Lack of correlations between penile thermography and pelvic arteriography in 29 cases of erectile impotence. J Urol. 1982;128(2):298–9.
68. Buvat J, Lemaire A, Buvat-Herbaut M, et al. Comparative investigations in 26 impotent and 26 nonimpotent diabetic patients. J Urol. 1985; 133(1):34–8.
69. Ramanathan R, Mulhall J, Rao S, et al. Predictive correlation between the International Index of Erectile Function (IIEF) and Sexual Health Inventory for Men (SHIM): implications for calculating a derived SHIM for clinical use. J Sex Med. 2007;4(5):1336–44.
70. Yeung AC, Leon MB, Jain A, et al. Clinical evaluation of the resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the resolute us clinical trial. J Am Coll Cardiol. 2011;57(17):1778–83.
71. Gray RR, Keresteci AG, St Louis EL, et al. Investigation of impotence by internal pudendal angiography: experience with 73 cases. Radiology. 1982;144(4):773–80.
72. Schwartz AN, Freidenberg D, Harley JD, et al. Nonselective angiography after intracorporal papaverine injection: an alternative technique for evaluating penile arterial integrity. Radiology. 1988;167(1): 249–53.
73. Kim ED, Owen RC, White GS, et al. Endovascular treatment of vasculogenic erectile dysfunction. Asian J Androl. 2014. doi: 10.4103/1008-682X.143752. [Epub ahead of print].
74. Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10,004 patients with surveillance angiography. Heart. 2014;100(2):153–9.
75. Alfonso F, Byrne RA, Rivero F, et al. Current treatment of in-stent restenosis. J Am Coll Cardiol. 2014;63(24):2659–73.
76. Remkes WS, Somi S, Roolvink V, et al. Direct drug-eluting stenting to reduce stent restenosis: a randomized comparison of direct stent implantation to conventional stenting with pre-dilation or provisional stenting in elective PCI patients. JACC Cardiovasc Interv. 2014;7(7):751–8.
77. Nojima Y, Yasuoka Y, Kume K, et al. Switching types of drug-eluting stents does not prevent repeated in-stent restenosis in patients with coronary drug-eluting stent restenosis. Coron Artery Dis. 2014;25(8): 638–44.
78. Philip F, Shishehbor MH, Desai MY, et al. Characterization of internal pudendal artery atherosclerosis using aortography and multi-detector computed angiography. Catheter Cardiovasc Interv. 2013;82(4):E516–21.
79. Aversa A, Sarteschi LM. The role of penile color-duplex ultrasound for the evaluation of erectile dysfunction. J Sex Med. 2007;4(5):1437–47.
80. Valji K, Bookstein JJ. Diagnosis of arteriogenic impotence: efficacy of duplex sonography as a screening tool. Am J Roentgenol. 1993;160(1):65–9.
81. Quam JP, King BF, James EM, et al. Duplex and color Doppler sonographic evaluation of vasculogenic impotence. Am J Roentgenol. 1989;153(6):1141–7.
82. Spiliopoulos S, Shaida N, Katsanos K, et al. The role of interventional radiology in the diagnosis and management of male impotence. Cardiovasc Intervent Radiol. 2013;36(5):1204–12.
83. Wang TD, Lee WJ, Yang SC, et al. Safety and six-month durability of angioplasty for isolated penile artery stenoses in patients with erectile dysfunction: a first-in-man study. EuroIntervention. 2014;10(1): 147–56.
84. Pereira JA, Bilhim T, Rio Tinto H, et al. Radiologic anatomy of vasculogenic erectile dysfunction: a systematized approach. Acta Med Port. 2013;26(3): 219–25.
85. Izumi K, Kawanishi Y, Muguruma H, et al. Virtual cavernoscopy: a novel diagnostic tool for use in the corpus cavernosal lumen in patients with erectile dysfunction. BJU Int. 2011;108(8):1316–20.
86. Pretorius ES, Siegelman ES, Ramchandani P, et al. MR imaging of the penis. Radiographics. 2001; 21:S283–99.
87. John H, Kacl GM, Lehmann K, et al. Clinical value of pelvic and penile magnetic resonance angiography in preoperative evaluation of penile revascularization. Int J Impot Res. 1999;11(2):83–6.
88. Yamaki K, Saga T, Doi Y, et al. A statistical study of the branching of the human internal iliac artery. Kurume Med J. 1998;45(4):333–40.
89. Bilhim T, Pereira JA, Fernandes L, et al. Angiographic anatomy of the male pelvic arteries. Am J Roentgenol. 2014;203(4):W373–82.
90. Herman A, Adar R, Rubinstein Z. Vascular lesions associated with impotence in diabetic and nondiabetic arterial occlusive disease. Diabetes. 1978;27(10): 975–81.
91. Struyven J, Gregoir W, Giannakopoulos X, et al. Selective pudendal arteriography. Eur Urol. 1979;5(4):233–42.
92. Nessi R, De Flaviis L, Bellinzoni G, et al. Digital angiography of erectile failure. Br J Urol. 1987;59(6):584–9.

The Effect of Radical Prostatectomy on Sexual Function

17

Lawrence C. Jenkins and John P. Mulhall

Prevalence of ED After RP

Review of Literature

Erectile dysfunction (ED) is an expected consequence of radical prostatectomy (RP) surgery. However, the rates of ED are very discrepant. In a meta-analysis performed by Tal et al., 22 studies were included encompassing nearly 5000 patients in order to evaluate the rate of erectile function recovery (EFR) [1]. There were 212 studies identified; however, only 22 met the strict inclusion criteria for evaluation of EFR. They found an overall EFR of 58 %, and when limited to studies reporting at least 18-month follow-up, the EFR increased to 60 %. There were also slight differences in EFR related to surgical method: open radical prostatectomy (RRP) (57 %), laparoscopic radical prostatectomy (LRP) (58 %), and robot-assisted radical prostatectomy (RARP) (73 %). However, they concluded that the compendium of literature regarding prostatectomy outcomes had significant heterogeneity in definitions of erectile function, which makes it very difficult to compare studies and summarize results. A meta-analysis by Ficarra et al. identified six studies comparing RARP to RRP and four studies comparing RARP to LRP [2]. The 12- and 24-month erectile function recovery (EFR) rates ranged from 54–90 to 63–94 %, respectively. Table 17.1 shows a sampling of recent prevalence studies [3–13].

Discrepancies

As Tal et al. demonstrated in their meta-analysis, there is significant heterogeneity of studies reporting EFR outcomes [1]. Studies not only differ on how they define EFR, but there are many differences in the study design, reporting of data, reporting on the frequency of the use of phosphodiesterase 5 inhibitors (PDE5i) or intracavernosal injection (ICI) therapy, duration of follow-up, surgical technique, and exclusion of neoadjuvant/adjuvant treatments. There is no standardization in the reporting of post-prostatectomy erectile function outcomes, and until this exists, there will be great difficulty comparing studies and extrapolating data for treatment decision-making. The American Urological Association Clinically Localized Prostate Cancer Guideline Committee recommends that clinical trials include the prospective accrual of data in regard to the pretreatment

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Table 17.1 Recent prevalence studies

Reference	Approach	No. evaluable	Mean (median) age	Minimum months of follow-up	Collection method	Definition of erectile function recovery	Baseline erectile function (%)	Baseline erectile function without PDE5i (%)	Erectile function recovery (%)	Erectile function without erectogenic medications after RP (%)
Woo [3]	RARP	483		12	SHIM	SHIM > 21	67.10	48.10	79.7	41.20
Gandaglia [4]	RARP-BNS	315	61.2	24	IIEF-EF	IIEF-EF ≥ 22			67.8	
	ORP-BNS	294	61.3	24	IIEF-EF	IIEF-EF ≥ 22			52.1	
Fode [5]	RRP	142	[66]	12	IIEF-5	≥17 with/without PDE5i			28.9	
	RARP	182	[65]	12	IIEF-5	≥17 with/without PDE5i			36.3	
Xylinas [6]	RARP	500	62.2	24	IIEF-5	Penetration with/without PDE5i	100	100	63	37
Verze [7]	ELP-BNS	128	65.3	24	IIEF	Not reported			82	
Tewari [8]	RARP	1100	58	12	IIEF-5	≥4 on Q2 with/without PDE5i			88[a]	
Resnick [9]	RP	1164	[64]	24	Interview	Erection insufficient for intercourse			21.2	
Ploussard [10]	ERARP	792	63	24	IIEF-5	With/without PDE5i			60.9	
Ludovico [11]	RARP-BNS	82	68.1	12	IIEF-5	>22			26.9	
	RP-BNS	48	66.7	12	IIEF-5	>22			25	
Ficarra [12]	RARP	110	62.3	12	IIEF-5	>17			85	47.30
Yip [13]	RARP	83	66.4	12	Interview	Erection hard enough for penetration with/without PDE5i			91.5	54.20

ELP extraperitoneal laparoscopic prostatectomy, *ERARP* extraperitoneal robot-assisted radical prostatectomy
[a]Calculated value

level of erectile function using validated self-report instruments and serial long-term follow-up be utilized to assess the changes in function [14]. However, the committee did not standardize the exact instrument or length of follow-up which continues to allow for variability in reporting outcomes.

Open Versus Laparoscopic Versus Robot-Assisted

In a recent prospective non-randomized study of 2431 men comparing open (RRP) and robot-assisted (RARP) radical prostatectomy, evaluating outcomes in the first 12 months found that erectile dysfunction was present in 70 % of men 12 months after RARP and 75 % of men after RRP [15]. The Ficarra et al. meta-analysis showed that RARP had better 12-month EFR rates compared to RRP (odds ratio [OR], 2.84; 95 % confidence interval [CI], 1.46–5.43; $p = 0.002$) [2]. EFR was defined in the following ways: erection sufficient for intercourse with or without the use of PDE5i (five studies) and Sexual Health Inventory for Men (SHIM) score >17 (one study). When they compared RARP versus LRP using four studies, they found a non-statistically significant trend toward better EFR at 12 months when compared to RARP. In these four studies, EFR was defined as erection sufficient for intercourse (with or without a PDE5i).

In a study by Kim et al., patients' functional outcomes were evaluated prospectively after RRP (235 patients) and RARP (528 patients) [16]. EFR was defined as erections sufficient for intercourse (with or without a PDE5i). They found that patients who underwent a RARP regained EF much more rapidly than those who underwent an RRP. However, the biggest criticisms of this study are not only the non-randomized nature, but there were significantly more patients in the RRP group who received neoadjuvant treatments which have been known to effect EF outcomes [17]. In a study by Krambeck et al., patients were matched 2:1 to RRP (492 patients) or RARP (248 patients) for age, preoperative serum PSA level, surgical period, clinical stage, and grade [18]. EF was evaluated at 12 months postoperatively, and there was no significant difference ($p = 0.081$) between the two groups; however, there was a trend toward increased EFR in the RARP group (70 %) over the RRP group (62.8 %).

As mentioned earlier, Tal et al. identified 22 articles for their meta-analysis; within these, there were 9965 subjects; however, there were only 4983 with appropriate ED data available [1]. They found that when the length of follow-up was ≥18 months, the EFR was 60 %, and when it was <18 months, it was 56 %, thus illustrating that longer follow-up is necessary to fully interpret data. Of the 22 articles, 19 were single-center series with EFR rates of 60 %, which was significantly higher than the 3 multicenter series with EFR rates of 33 %. Mulhall also found in his review of ED literature that studies with the highest EF recovery rates came from single-center series and those with the lowest came from the multicenter series [19]. He stated that it was unclear whether this was due to single centers being centers of excellence or that the multicenter series assessed different patient populations. An example was given: multicenter series have used SEER/Medicare data which involves patients typically older than the average age for single-center series and thus skews their recovery data negatively.

ED Outcomes After RP

With so many articles present on ED outcomes after RP, yet no standardization in reporting, one must understand that caution should be exercised when reviewing the literature. Table 17.2 identifies many of the factors important in defining and reporting outcomes [19].

In a study by Sanda et al., patient quality of life was evaluated prospectively with prostate cancer treatment [20]. They included 603 patients post-RP and followed them for 24 months. They found that changes in quality of life significantly affect satisfaction with the overall outcome in both the patient and partner. They also found that age, PSA score, and nerve-sparing status were associated with quality of life scores after RP.

Table 17.2 Factors important in defining and reporting outcomes

Study population
Population demographics
Data acquisition method
Variability in questionnaire selection
Timing of EF assessment
Baseline erectile function
Patient comorbidity profile
Operative considerations—nerve-sparing status
Definition of an adequate erection
Quality of the erections
Consistency of the erections
The use of erectile aids

Definition

Erectile dysfunction is defined by the National Institutes of Health as "the consistent inability to obtain and/or maintain an erection for satisfactory sexual intercourse" [21]. Many outcome studies expand their definition to allow the use of PDE5i, although they may not report this or count those patients separately from those not requiring medication for erectile function. There may also be differences of opinion on how to judge adequate erectile function, whether a cutoff on a questionnaire or patient self-report, introducing subjectivity and the risk for error. Patients want a return in the ability to obtain an erection, but many want the same hardness that they were able to achieve preoperatively [22, 23]. In a study by Nelson et al., 22 % of the sample population of 180 men had returned back to their baseline (preoperative) EF at 24-month post-RP without the use of PDE5i. Only 16 % of men with functional erections (International Index of Erectile Function [IIEF] erectile function domain score >24 out of 30) before surgery returned back to their baseline without the use of medication [24].

Data Acquisition

The means by which data are acquired within studies should minimize potential bias and be standardized through the use of validated questionnaires. The patient should be given a validated questionnaire prior to surgery, and the same questionnaire should be given serially afterward to maintain continuity within the data. The most common questionnaires used are the IIEF, the IIEF-6 (a shorter version of the IIEF encompassing only questions 1–5 and 15), the IIEF-5 (the SHIM), and the UCLA-Prostate Cancer Index (PCI) and the Expanded Prostate Cancer Index Composite (EPIC) [25–28]. Other problems include the following: some of these questionnaires are not validated for RP patients (IIEF, SHIM); some inquire about ejaculation, which RP patients will not experience; some are focused on bother as much as function (PCI, EPIC); some have no cutoffs for grading ED severity (PCI, EPIC); and some ask about activity in the past 4 weeks (IIEF) when patients often have been inactive during that time period.

Outcome studies must have a long enough follow-up period to show accurate results. In a study by Rabbani et al., they showed that EFR may continue beyond 24-month post-prostatectomy [29]. Also, in another study, the immediate post-prostatectomy EFR declined over the first 3 months, believed to be related to Wallerian degeneration in the cavernous nerves [30]. Wallerian degeneration is a process which occurs after a nerve is injured (cut or crush) and the distal component of the compromised axon begins to degenerate [31]. This process typically begins within 12–24 h of the injury. Baseline erectile function is related to long-term EFR as shown by Rabbani et al. [32, 33]. Patients with poor baseline erections do not perform as well as patients with good baseline erections. Outcome studies need to establish/report baseline erectile function and follow patients for at least 24 months.

Patient Population Studies

Factors such as age range, comorbidity profile, surgeon experience, or nerve-sparing status all factor into EFR and should be reported explicitly in outcome studies as they all impact on EFR after RP [19]. Younger patients have been shown to have better EFR outcomes after prostatectomy than their older counterparts [34].

Comorbidities and baseline EFR are very important factors in how a patient will recover EF after surgery, but they are not always reported. It has been established that patients undergoing nerve-sparing surgery do better, but this is also influenced by surgeon experience and volume [35–37]. A surgeon with a high volume of prostatectomies will tend to have better outcomes than their low-volume counterpart [38, 39].

The variations in outcome studies relate to the different factors mentioned above regarding study design and execution. We caution the reader to closely analyze studies to not misinterpret the data presented. EFR in excess of 90 % is not realistic for the general prostatectomist in the general population. Patient selection is a critical factor in this regard. If the surgeon chooses to present data on only the youngest patients with perfect baseline erections and perfect nerve-sparing surgery with the use of erectile aids, such figures are attainable but not in the general population. Until there is standardization in reporting erectile function outcome data, there will continue to be significant variances in reported data.

Pathophysiology of ED After RP

ED after RP is caused by several different mechanisms including neurogenic, smooth muscle damage and/or alterations in cavernosal oxygenation. Often the cause of ED is multifactorial; see Fig. 17.1.

Neurogenic Mechanisms

It is well recognized that injury to the cavernous nerves during prostatectomy will result in a direct loss of erectile function after surgery. Anatomic studies by Walsh et al. described how damage to the pelvic nerves during RP leads to ED [40, 41]. With the advent of nerve-sparing surgery, these outcomes have changed for the better; however, they are far from perfect [42, 43]. Patients undergoing bilateral nerve-sparing (BNS) surgery have better outcomes than those undergoing non-nerve-sparing (NNS) or even unilateral nerve-sparing (UNS) surgery [37, 44, 45]. Such nomenclature is now considered historical as it is appreciated that nerve sparing is incremental and it is gradable [46].

Alterations in contemporary prostatectomy techniques including minimizing traction on the urethral catheter during the surgery can improve EF outcomes [47, 48]. Tewari et al. performed a study using intraoperative penile oxygen saturation monitoring to assess vascular compromise to the penis during prostatectomy [49]. In his study, 64 patients underwent intraoperative monitoring, and they were matched with 192 patients who did not. They found that drops in oxygen saturation were associated with opening the endopelvic fascia, nerve-sparing steps, and whenever significant traction was placed on the catheter, seminal vesicles, or prostate during apical dissection. They reported that 94 % of patients in the monitoring group who had nerve-sparing surgery had a SHIM score of ≥17 at 12-month post-surgery compared to 78 % in the unmonitored group.

It is important to understand that EF may not be immediately affected after surgery and may continue to decline over the first 3 months after surgery. Katz et al. showed that 20 % of patients who had functional erections at month 3 lost those erections by month 6 [30]. However, when evaluated at month 12, that number improved to 9 % overall who continued to have nonfunctional erections. The authors suggested that there may be ongoing inflammatory changes leading to Wallerian degeneration causing delayed cavernosal nerve injury. This cavernosal nerve damage leads to corporal smooth muscle and endothelial changes that will be explained later.

Smooth Muscle Damage

Corporal smooth muscle changes such as increased collagenization, and apoptosis can lead to corporal veno-occlusive dysfunction (CVOD or venous leak). Neural trauma during prostatectomy leads to a reflex alteration in corpus cavernosal smooth muscle and endothelial structure. This is amplified by the often prolonged absence of erections after this operation.

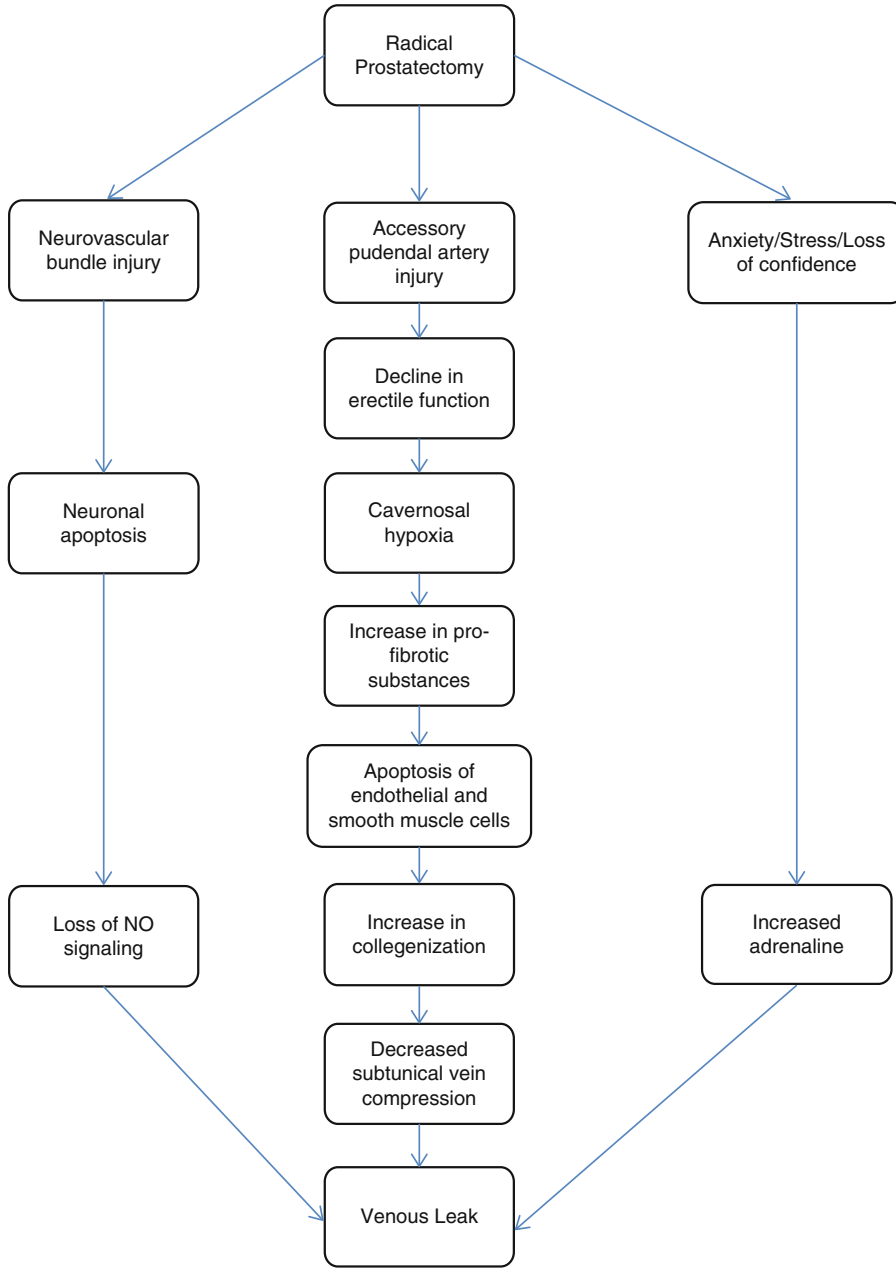

Fig. 17.1 The multifactorial causes/pathophysiology of ED after radical prostatectomy

Erectile dysfunction leads to decreased oxygen tension within the corpora, causing the inhibition of prostaglandin E1 (PGE1), which normally inhibits pro-fibrotic substances like TGF-β1. Therefore, TGF-β1 results in replacement of the cavernosal smooth muscle by collagen. Multiple rat models have shown that this process occurs rapidly after cavernosal nerve injury, all studies detailing increased collagen content and decreased smooth muscle-collagen ratios after injury [50, 51].

Some of the first research on apoptosis in the rat nerve injury model was done by Klein et al. They examined the rat penile tissue in 15 subjects

after bilateral cavernous neurotomy and another 15 sham-operated controls [52]. In the nerve injury models, they found significantly higher amounts of apoptotic cells compared to the controls. In a study by User et al., rat models with bilateral or unilateral cavernous nerve injuries were used to show differences in penile weight, DNA protein, and apoptosis at selected time points [53]. Bilateral neurotomy resulted in significantly more damage compared to unilateral including loss of penile weight, DNA protein, and apoptosis. They also showed that the subtunical smooth muscle cells were the most highly affected. The authors proposed that this change in sub-tunical smooth muscle density may be part of the mechanism for CVOD. In a study by Lysiak et al., mice models with cavernous neurotomy or sham surgery were used to show apoptosis. They were able to immunolocalize signs of apoptosis in both endothelial and smooth muscle cells within the penis. Several studies have looked at the type of cavernous nerve injury and the resulting effects. These animal models were attempts to closely approximate the effects of RP using techniques such as transection, crush, and freezing of the cavernous nerves [54].

A study by Iacono et al. examined human corpora cavernosal biopsies before and after RP to identify the tissue content [55]. Overall, 19 patients participated in the study, and postoperative biopsies were performed at the 2- and 12-month visits. In the postoperative biopsies, they found that the smooth muscle and elastic fiber content were both significantly decreased and the collagen content was significantly increased at both time points when compared to the previous biopsy.

Cavernosal Oxygenation

Arterial injury may play a role in the events leading to erectile dysfunction after RP. The accessory pudendal arteries (APAs) generally arise above the levator ani muscles and travel toward the perineum [56, 57]. The prevalence rate of APAs is variable, but their presence has been shown to provide a significant blood supply to the corpora cavernosal arteries [58–61]. In one study, 33 APAs were identified in 20 cadavers, and they were the only source of penile arterial inflow in 15 % of subjects [60]. Droupy et al. utilized pharmacologically induced erections and transrectal ultrasound imaging to show hemodynamic changes in APAs similar to the cavernosal arteries and no changes in other pelvic vessels. This signifies that the APAs are closely related to the penile blood flow.

Preservation of APAs during RP was examined by Rogers et al., and they found that patients who had APA preservation had a significantly decreased median time for EF recovery, 6 versus 12 months [59]. However, Box et al. found no significant correlation related to APA preservation and erectile function when using multivariate analysis [62].

The absence of cavernosal oxygenation can lead to the same negative chain of events as nerve injury: inhibition of PGE1 and increased profibrotic cytokines leading to increased collagen deposition. In a series of studies by Moreland et al., they have shown that in in vitro experiments, exposure of the corporal smooth muscle to low oxygen conditions leads to suppression of PGE1 and cAMP production and upregulation of TGF-beta [63–65]. In the post-RP patient with chronic ED, the lack of the natural erection cycles leads to an overall chronic hypoxic condition causing irreversible structural changes.

Venous Leak

Corporal veno-occlusive dysfunction or venous leak results from a failure of the corporal smooth muscle to compress the sub-tunical venules against the tunica albuginea to stop the outflow of blood during an erection. When the venules are not compressed, blood escapes from the penis, thereby limiting the ability to obtain and/or maintain an erection. As discussed earlier, Iacono et al. performed corpora cavernosal biopsies before and after RP and found smooth muscle and elastic fiber deficits and increased collagen deposition as early as 2 months after surgery [55]. The Goldstein group showed using human cavernosal biopsy

that when smooth muscle content drops below 40 %, venous leak occurs [66]. In a subsequent study, Tal et al. showed that RP nerve-sparing status is associated with the likelihood for developing venous leak [37]. In their study, they found venous leak prevalence at 6 months after RP to be 7, 11, and 75 % in BNS, UNS, and NNS surgeries, respectively. They also found that the only patients to have venous leak at 3 months were those who underwent non-nerve-sparing surgery.

Venous leak is therefore an end result of multiple events set into play after RP. This multifactorial process involving nerve injury, arterial injury, and decreased cavernosal oxygenation leads to increased fibrotic changes within the corpora cavernosa. Decreased smooth muscle and elastic fiber content and increased collagen deposition result in CVOD and therefore permanent ED. At this time, there is no means of reversing venous leak, and thus, rehabilitation strategies are aimed at reducing the likelihood of venous leak development. Whether the highly anticipated introduction of stem cell therapy for ED in the future can achieve venous leak reversal has been discussed but remains to be seen.

Non-ED Sexual Dysfunctions After RP

There are other non-ED sexual dysfunctions which often receive less attention but still cause significant patient and partner bother. These sexual dysfunctions are often related to orgasm including changes in orgasm intensity, sexual incontinence, and orgasmic pain (dysorgasmia). Most patients are unaware of these side effects prior to surgery. In a study of 256 sexually active patients after RP, 65 % reported decreased orgasm intensity or anorgasmia, and 9 % experienced pain with orgasm [67].

Sexual Incontinence

Climacturia

Climacturia defined as urinary incontinence at orgasm can be a very bothersome and surprising experience for the patient and partner when they return to having sexual relations. In a study of 42 patients, an average of 24 months after radical prostatectomy, 45 % reported climacturia [68]. However, only 48 % reported significant bother, and only 21 % reported that it was a significant bother for their partners. In a study of 475 patients, 20 % reported climacturia after radical pelvic surgery [69]. Climacturia was more common in the first 12 months after surgery and in those who also reported orgasmic pain. It was less common in patients after cystoprostatectomy when compared to open or laparoscopic prostatectomy groups. In a survey of 279 patients after radical prostatectomy, 28 % reported to have climacturia at a median time since surgery of 20 months [70]. Also of interest, urinary incontinence was almost twice as common in those with climacturia (64 %) compared to those without (33 %). In a study of 1358 men who had a radical prostatectomy by a single surgeon, 44 % reported incontinence during sexual activity at 3 months, and this declined to 36 % at 24 months [71]. The bother rate also declined from 22 % at 3 months to 12 % at 24 months. In a study of 691 sexually active men after RP, 33 % reported climacturia who were otherwise continent. See Table 17.3 [68–74].

Treatment options for climacturia are limited; however, advising patients to empty their bladder prior to sexual activity is routine counsel. Other strategies include using a condom or a variable tension loop to occlude the urethra. In a study of 124 patients with climacturia after RP who used a variable tension loop, 84 % of patients reported moderate or large volume climacturia at baseline compared to 26 % at follow-up (mean 6 months) [75]. When patients were asked about the frequency of their climacturia, at baseline, they reported their experience as rare 15 %, occasional 48 %, most of the time 16 %, or always 21 %. With the use of the variable tension loop, patients reported their experiences as none 48 %, rarely 34 %, or occasionally 28 %. Even without treatment, climacturia generally dissipates over the first 2 years after RP.

Arousal Incontinence

Arousal incontinence is not very well studied but is known to occur with erection or sexual stimulation prior to orgasm. Anecdotally, this typically

Table 17.3 Climacturia studies

Author	Year	Op	Patient #	Climacturia (%)	Outcomes
O'Neil [70]	2014	RP	219	28	Predictors—the use of any erectile aide, urinary incontinence
Manassero [72]	2013	RP	84	29	Functional urethral length < control
Mitchell [71]	2011	RP	1152	36	Did not differentiate between arousal and orgasm incontinence
Choi [69]	2007	RP	475	20	ORP > LRP
Lee [68]	2006	RP	42	45	50 % men bothered
					25 % partners bothered
Abouassaly [73]	2006	RP	26	N/A	Large volume variability
Koeman [74]	1996	RP	17	64	

ORP open radical prostatectomy, *LRP* laparoscopic radical prostatectomy

is more common in the first few months immediately after RP and improves with time. In a study of 24 men who had no daytime incontinence, 38 % of men experienced the loss of urine during kissing, hugging, or genital foreplay [76]. All patients reported some level of bother and embarrassment, and 6 of the 24 men were avoiding sexual contact.

Orgasmic Pain and Other Changes in Orgasm

Orgasmic pain or dysorgasmia has been reported at rates ranging from 3 to 19 % of patients [77]. In a study of 239 men after RP via questionnaire, 22 % of patients had no change in orgasm, 37 % had anorgasmia, 37 % had decreased orgasm intensity, and 4 % had increased orgasm intensity [78]. In this same group of men, dysorgasmia was reported in 14 % of patients with 63 % stating the primary location was in the penis, and 33 % stated the pain occurred with every orgasm. In a study of 63 patients after RP, 52 % reported a decrease in sexual desire, 78 % reported a decrease in orgasm (40 % anorgasmia), and 8 % reported an increase in orgasm [79]. In a study of 691 sexually active men after RP, 19 % reported orgasmic pain at a mean follow-up of 2.2 years [80].

In a study of 98 patients with orgasmic pain (34 had undergone RP), patients were treated with tamsulosin 0.4 mg for at least 4 weeks; 77 % of patients reported significant relief and 12 % reported complete resolution of their pain [81]. However, there was no placebo group for this trial. The idea behind this treatment relates to the pain being triggered by spasm of the vesicourethral anastomosis and therefore the pelvic floor musculature. This pelvic floor muscle spasm or increased tone has also been associated with chronic pelvic pain syndrome [82]. It has been suggested that there may be an association with seminal vesicle (SV)-sparing RP and dysorgasmia. This was reported by one study of RP patients where 144 men had bilateral SV sparing, 91 underwent unilateral SV sparing, and 67 had complete removal of the SVs; 21, 12, and 9 %, respectively, reported dysorgasmia [83]. The bilateral SV-sparing procedure had a significant RR of dysorgasmia when compared to bilateral removal (RR 2.33, 95 % CI 1.0–5.3, $p = 0.045$).

These sexual dysfunctions are often overlooked by the surgeon as not being major risks, but they can have devastating impacts to the patient. We encourage full disclosure to make sure that the patient has an adequate expectation of their quality of life after surgery.

References

1. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med. 2009;6(9):2538–46.
2. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, Graefen M, et al. Systematic review and

meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol. 2012;62(3):418–30.
3. Woo SH, Kang DI, Ha YS, Salmasi AH, Kim JH, Lee DH, et al. Comprehensive analysis of sexual function outcome in prostate cancer patients after robot-assisted radical prostatectomy. J Endourol. 2014;28(2):172–7.
4. Gandaglia G, Suardi N, Gallina A, Zaffuto E, Cucchiara V, Vizziello D, et al. How to optimize patient selection for robot-assisted radical prostatectomy: functional outcome analyses from a tertiary referral center. J Endourol. 2014;28(7):792–800.
5. Fode M, Sonksen J, Jakobsen H. Radical prostatectomy: initial experience with robot-assisted laparoscopic procedures at a large university hospital. Scand J Urol. 2014;48(3):252–8.
6. Xylinas E, Durand X, Ploussard G, Campeggi A, Allory Y, Vordos D, et al. Evaluation of combined oncologic and functional outcomes after robotic-assisted laparoscopic extraperitoneal radical prostatectomy: trifecta rate of achieving continence, potency and cancer control. Urol Oncol. 2013;31(1):99–103.
7. Verze P, Scuzzarella S, Martina GR, Giummelli P, Cantoni F, Mirone V. Long-term oncological and functional results of extraperitoneal laparoscopic radical prostatectomy: one surgical team's experience on 1,600 consecutive cases. World J Urol. 2013; 31(3):529–34.
8. Tewari AK, Ali A, Metgud S, Theckumparampil N, Srivastava A, Khani F, et al. Functional outcomes following robotic prostatectomy using athermal, traction free risk-stratified grades of nerve sparing. World J Urol. 2013;31(3):471–80.
9. Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368(5):436–45.
10. Ploussard G, Salomon L, Parier B, Abbou CC, de la Taille A. Extraperitoneal robot-assisted laparoscopic radical prostatectomy: a single-center experience beyond the learning curve. World J Urol. 2013; 31(3):447–53.
11. Ludovico GM, Dachille G, Pagliarulo G, D'Elia C, Mondaini N, Gacci M, et al. Bilateral nerve sparing robotic-assisted radical prostatectomy is associated with faster continence recovery but not with erectile function recovery compared with retropubic open prostatectomy: the need for accurate selection of patients. Oncol Rep. 2013;29(6):2445–50.
12. Ficarra V, Borghesi M, Suardi N, De Naeyer G, Novara G, Schatteman P, et al. Long-term evaluation of survival, continence and potency (SCP) outcomes after robot-assisted radical prostatectomy (RARP). BJU Int. 2013;112(3):338–45.
13. Yip KH, Yee CH, Ng CF, Lam NY, Ho KL, Ma WK, et al. Robot-assisted radical prostatectomy in Hong Kong: a review of 235 cases. J Endourol. 2012; 26(3):258–63.
14. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol. 2007;177(6):2106–31.
15. Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderang U, Thorsteinsdottir T, et al. Urinary incontinence and erectile dysfunction after robotic versus open radical prostatectomy: a prospective, controlled, nonrandomised trial. Eur Urol. 2015;68(2):216–25.
16. Kim SC, Song C, Kim W, Kang T, Park J, Jeong IG, et al. Factors determining functional outcomes after radical prostatectomy: robot-assisted versus retropubic. Eur Urol. 2011;60(3):413–9.
17. Mazzola CR, Deveci S, Heck M, Mulhall JP. Androgen deprivation therapy before radical prostatectomy is associated with poorer postoperative erectile function outcomes. BJU Int. 2012;110(1):112–6.
18. Krambeck AE, DiMarco DS, Rangel LJ, Bergstralh EJ, Myers RP, Blute ML, et al. Radical prostatectomy for prostatic adenocarcinoma: a matched comparison of open retropubic and robot-assisted techniques. BJU Int. 2009;103(4):448–53.
19. Mulhall JP. Defining and reporting erectile function outcomes after radical prostatectomy: challenges and misconceptions. J Urol. 2009;181(2):462–71.
20. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008;358(12):1250–61.
21. NIH Consensus Conference. Impotence: NIH consensus development panel on impotence. JAMA. 1993;270(1):83–90.
22. Mulhall JP, Levine LA, Junemann KP. Erection hardness: a unifying factor for defining response in the treatment of erectile dysfunction. Urology. 2006;68(3 Suppl):17–25.
23. Goldstein I, Mulhall JP, Bushmakin AG, Cappelleri JC, Hvidsten K, Symonds T. The erection hardness score and its relationship to successful sexual intercourse. J Sex Med. 2008;5(10):2374–80.
24. Nelson CJ, Scardino PT, Eastham JA, Mulhall JP. Back to baseline: erectile function recovery after radical prostatectomy from the patients' perspective. J Sex Med. 2013;10(6):1636–43.
25. 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(6):822–30.
26. Cappelleri JC, Rosen RC. The sexual health inventory for men (SHIM): a 5-year review of research and clinical experience. Int J Impot Res. 2005;17(4):307–19.
27. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA prostate cancer index: development, reliability, and validity of a health-related quality of life measure. Med Care. 1998;36(7):1002–12.
28. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded

prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56: 899–905.
29. Rabbani F, Schiff J, Piecuch M, Yunis LH, Eastham JA, Scardino PT, et al. Time course of recovery of erectile function after radical retropubic prostatectomy: does anyone recover after 2 years? J Sex Med. 2010;7(12):3984–90.
30. Katz D, Bennett NE, Stasi J, Eastham JA, Guillonneau BD, Scardino PT, et al. Chronology of erectile function in patients with early functional erections following radical prostatectomy. J Sex Med. 2010;7(2 Pt 1): 803–9.
31. Wang L, Sanford MT, Xin Z, Lin G, Lue TF. Role of Schwann cells in the regeneration of penile and peripheral nerves. Asian J Androl. 2015;17(5): 776–82.
32. Rabbani F, Stapleton AM, Kattan MW, Wheeler TM, Scardino PT. Factors predicting recovery of erections after radical prostatectomy. J Urol. 2000;164(6): 1929–34.
33. Teloken PE, Nelson CJ, Karellas M, Stasi J, Eastham J, Scardino PT, et al. Defining the impact of vascular risk factors on erectile function recovery after radical prostatectomy. BJU Int. 2013;111(4):653–7.
34. Muller A, Parker M, Waters BW, Flanigan RC, Mulhall JP. Penile rehabilitation following radical prostatectomy: predicting success. J Sex Med. 2009;6(10):2806–12.
35. Bianco Jr FJ, Vickers AJ, Cronin AM, Klein EA, Eastham JA, Pontes JE, et al. Variations among experienced surgeons in cancer control after open radical prostatectomy. J Urol. 2010;183(3):977–82.
36. Vickers A, Savage C, Bianco F, Mulhall J, Sandhu J, Guillonneau B, et al. Cancer control and functional outcomes after radical prostatectomy as markers of surgical quality: analysis of heterogeneity between surgeons at a single cancer center. Eur Urol. 2011;59(3):317–22.
37. Tal R, Valenzuela R, Aviv N, Parker M, Waters WB, Flanigan RC, et al. Persistent erectile dysfunction following radical prostatectomy: the association between nerve-sparing status and the prevalence and chronology of venous leak. J Sex Med. 2009;6(10):2813–9.
38. Bianco Jr FJ, Riedel ER, Begg CB, Kattan MW, Scardino PT. Variations among high volume surgeons in the rate of complications after radical prostatectomy: further evidence that technique matters. J Urol. 2005;173(6):2099–103.
39. Wilson A, Marlow NE, Maddern GJ, Barraclough B, Collier NA, Dickinson IC, et al. Radical prostatectomy: a systematic review of the impact of hospital and surgeon volume on patient outcome. ANZ J Surg. 2010;80(1–2):24–9.
40. Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. Prostate. 1983; 4(5):473–85.
41. Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol. 1982;128(3):492–7.
42. Quinlan DM, Epstein JI, Carter BS, Walsh PC. Sexual function following radical prostatectomy: influence of preservation of neurovascular bundles. J Urol. 1991; 145(5):998–1002.
43. Marien T, Sankin A, Lepor H. Factors predicting preservation of erectile function in men undergoing open radical retropubic prostatectomy. J Urol. 2009;181(4): 1817–22.
44. Catalona WJ, Carvalhal GF, Mager DE, Smith DS. Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. J Urol. 1999;162(2):433–8.
45. Walsh PC, Partin AW, Epstein JI. Cancer control and quality-of-life following anatomical radical retropubic prostatectomy—results at 10 years. J Urol. 1994;152(5):1831–6.
46. Moskovic DJ, Alphs H, Nelson CJ, Rabbani F, Eastham J, Touijer K, et al. Subjective characterization of nerve sparing predicts recovery of erectile function after radical prostatectomy: defining the utility of a nerve sparing grading system. J Sex Med. 2011;8(1):255–60.
47. Masterson TA, Serio AM, Mulhall JP, Vickers AJ, Eastham JA. Modified technique for neurovascular bundle preservation during radical prostatectomy: association between technique and recovery of erectile function. BJU Int. 2008;101(10):1217–22.
48. Chauhan S, Coelho RF, Rocco B, Palmer KJ, Orvieto MA, Patel VR. Techniques of nerve-sparing and potency outcomes following robot-assisted laparoscopic prostatectomy. Int Braz J Urol. 2010; 36(3):259–72.
49. Tewari A, Srivastava A, Sooriakumaran P, Grover S, Dorsey P, Leung R. Technique of traction-free nerve-sparing robotic prostatectomy: delicate tissue handling by real-time penile oxygen monitoring. Int J Impot Res. 2012;24(1):11–9.
50. Leungwattanakij S, Bivalacqua TJ, Usta MF, Yang DY, Hyun JS, Champion HC, et al. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. J Androl. 2003;24(2):239–45.
51. Ferrini MG, Davila HH, Kovanecz I, Sanchez SP, Gonzalez-Cadavid NF, Rajfer J. Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. Urology. 2006;68(2):429–35.
52. Klein LT, Miller MI, Buttyan R, Raffo AJ, Burchard M, Devris G, et al. Apoptosis in the rat penis after penile denervation. J Urol. 1997;158(2):626–30.
53. User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol. 2003;169(3):1175–9.
54. Canguven O, Burnett A. Cavernous nerve injury using rodent animal models. J Sex Med. 2008;5(8): 1776–85.

55. Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. J Urol. 2005;173(5): 1673–6.
56. Secin FP, Karanikolas N, Touijer AK, Salamanca JI, Vickers AJ, Guillonneau B. Anatomy of accessory pudendal arteries in laparoscopic radical prostatectomy. J Urol. 2005;174(2):523–6. discussion 6.
57. Mulhall JP, Secin FP, Guillonneau B. Artery sparing radical prostatectomy—myth or reality? J Urol. 2008;179(3):827–31.
58. Polascik TJ, Walsh PC. Radical retropubic prostatectomy: the influence of accessory pudendal arteries on the recovery of sexual function. J Urol. 1995;154(1):150–2.
59. Rogers CG, Trock BP, Walsh PC. Preservation of accessory pudendal arteries during radical retropubic prostatectomy: surgical technique and results. Urology. 2004;64(1):148–51.
60. Droupy S, Hessel A, Benoit G, Blanchet P, Jardin A, Giuliano F. Assessment of the functional role of accessory pudendal arteries in erection by transrectal color Doppler ultrasound. J Urol. 1999;162(6):1987–91.
61. Breza J, Aboseif SR, Orvis BR, Lue TF, Tanagho EA. Detailed anatomy of penile neurovascular structures: surgical significance. J Urol. 1989;141(2):437–43.
62. Box GN, Kaplan AG, Rodriguez Jr E, Skarecky DW, Osann KE, Finley DS, et al. Sacrifice of accessory pudendal arteries in normally potent men during robot-assisted radical prostatectomy does not impact potency. J Sex Med. 2010;7(1 Pt 1):298–303.
63. Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. Int J Impot Res. 1998;10(2): 113–20.
64. Moreland RB, Gupta S, Goldstein I, Traish A. Cyclic AMP modulates TGF-beta 1-induced fibrillar collagen synthesis in cultured human corpus cavernosum smooth muscle cells. Int J Impot Res. 1998;10(3): 159–63.
65. Moreland RB, Traish A, McMillin MA, Smith B, Goldstein I, Saenz de Tejada I. PGE1 suppresses the induction of collagen synthesis by transforming growth factor-beta 1 in human corpus cavernosum smooth muscle. J Urol. 1995;153(3 Pt 1):826–34.
66. Nehra A, Goldstein I, Pabby A, Nugent M, Huang YH, de las Morenas A, et al. Mechanisms of venous leakage: a prospective clinicopathological correlation of corporeal function and structure. J Urol. 1996; 156(4):1320–9.
67. Frey A, Sonksen J, Jakobsen H, Fode M. Prevalence and predicting factors for commonly neglected sexual side effects to radical prostatectomies: results from a cross-sectional questionnaire-based study. J Sex Med. 2014;11(9):2318–26.
68. Lee J, Hersey K, Lee CT, Fleshner N. Climacturia following radical prostatectomy: prevalence and risk factors. J Urol. 2006;176(6 Pt 1):2562–5. discussion 5.
69. Choi JM, Nelson CJ, Stasi J, Mulhall JP. Orgasm associated incontinence (climacturia) following radical pelvic surgery: rates of occurrence and predictors. J Urol. 2007;177(6):2223–6.
70. O'Neil BB, Presson A, Gannon J, Stephenson RA, Lowrance W, Dechet CB, et al. Climacturia after definitive treatment of prostate cancer. J Urol. 2014;191(1):159–63.
71. Mitchell SA, Jain RK, Laze J, Lepor H. Post-prostatectomy incontinence during sexual activity: a single center prevalence study. J Urol. 2011; 186(3):982–5.
72. Manassero F, Di Paola G, Paperini D, Mogorovich A, Pistolesi D, Valent F, et al. Orgasm-associated incontinence (climacturia) after bladder neck-sparing radical prostatectomy: clinical and video-urodynamic evaluation. J Sex Med. 2012;9(8):2150–6.
73. Abouassaly R, Lane BR, Lakin MM, Klein EA, Gill IS. Ejaculatory urine incontinence after radical prostatectomy. Urology. 2006;68(6):1248–52.
74. Koeman M, van Driel MF, Schultz WC, Mensink HJ. Orgasm after radical prostatectomy. Br J Urol. 1996;77(6):861–4.
75. Mehta A, Deveci S, Mulhall JP. Efficacy of a penile variable tension loop for improving climacturia after radical prostatectomy. BJU Int. 2013;111(3):500–4.
76. Guay A, Seftel AD. Sexual foreplay incontinence in men with erectile dysfunction after radical prostatectomy: a clinical observation. Int J Impot Res. 2008;20(2):199–201.
77. Frey AU, Sonksen J, Fode M. Neglected side effects after radical prostatectomy: a systematic review. J Sex Med. 2014;11(2):374–85.
78. Barnas JL, Pierpaoli S, Ladd P, Valenzuela R, Aviv N, Parker M, et al. The prevalence and nature of orgasmic dysfunction after radical prostatectomy. BJU Int. 2004;94(4):603–5.
79. Messaoudi R, Menard J, Ripert T, Parquet H, Staerman F. Erectile dysfunction and sexual health after radical prostatectomy: impact of sexual motivation. Int J Impot Res. 2011;23(2):81–6.
80. Nilsson AE, Carlsson S, Johansson E, Jonsson MN, Adding C, Nyberg T, et al. Orgasm-associated urinary incontinence and sexual life after radical prostatectomy. J Sex Med. 2011;8(9):2632–9.
81. Barnas J, Parker M, Guhring P, Mulhall JP. The utility of tamsulosin in the management of orgasm-associated pain: a pilot analysis. Eur Urol. 2005; 47(3):361–5. discussion 5.
82. Hetrick DC, Ciol MA, Rothman I, Turner JA, Frest M, Berger RE. Musculoskeletal dysfunction in men with chronic pelvic pain syndrome type III: a case-control study. J Urol. 2003;170(3):828–31.
83. Mogorovich A, Nilsson AE, Tyritzis SI, Carlsson S, Jonsson M, Haendler L, et al. Radical prostatectomy, sparing of the seminal vesicles, and painful orgasm. J Sex Med. 2013;10(5):1417–23.

The Effect of Radiation on Erectile Function

18

Kelly A. Chiles and John P. Mulhall

Assessing Erectile Function Outcomes After Radiation

Studies investigating erectile dysfunction (ED) are difficult to decipher for many reasons. Unfortunately, ED after radiation presents a uniquely challenging Gordian knot that is difficult to unravel. Because of the diversity in quality of studies, there is no solid outcome data which can be presented to patients to help them understand their individual risk of ED after their radiation regimen. Erectile function (EF) has been largely left out of most studies on radiation treatment outcomes, and those studies which include EF assessment utilize widely variable definitions. Many of these studies are retrospective and use subjective data without any controls or baseline erectile function (EF) assessment.

Validated tools such as the International Index of Erectile Function (IIEF) or abridged versions such as the IIEF-5 (Sexual Health Inventory For Men, SHIM) provide meaningful insights into EF, can define ED and grade it, yet often are not used in such outcome analyses [1, 2].

Specific to radiation trials, many studies pool heterogenous radiation regimens such as brachytherapy, external beam radiation therapy (EBRT), proton therapy with or without androgen deprivation therapy together despite the fact that there may be significant differences in sexual function outcomes. These differences stem not only from the fact that brachytherapy is unlike external beam radiation, but also from the fact that patients choosing different radiation delivery options are often quite different at baseline as well. In addition, patients who receive brachytherapy plus EBRT should not be combined with patients who received only one of those treatments, yet this pooling happens. There are also marked differences in seemingly similar radiation regimens, and the total radiation dose and the field could vary significantly across patients, particularly when comparing the myriad options for external beam radiation treatment.

The use of androgen deprivation therapy (ADT) unequivocally confounds any sexual function outcomes, and the timing and duration of ADT varies across institutional protocols because there is no single guiding standard. The median follow-up of studies varies widely. Radiation studies, given the pathophysiology of ED after RT, in particular need

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much longer follow-up (minimum of 3 years) than surgical interventions in order to provide meaningful data.

The field of radiation oncology continues to change with newly emerging technology, and this has allowed a constant evolution of radiation protocols that continually hone oncologic success. This evolution, however, means that outcome studies from prior years may no longer be relevant to current protocols, making any established ED rates similarly inapplicable. Salvage radiation and radiation used in conjunction with prostatectomy also need to be studied independently from primary radiation therapy. Finally, despite how poorly studied ED is within the radiation oncology literature, other sexual dysfunction sequelae such as sexual incontinence and orgasmic dysfunction are even more poorly defined.

Pathophysiology of ED After Radiation Treatment

A rigid erection results from the interplay between neural input (nervi erigentes initiate erections through release of nitric oxide), arterial inflow to the corpora (via the internal pudendal and accessory arteries), and the ability of the corporal smooth muscle to appropriately dilate and restrict venous outflow [3]. Pelvic radiation will expose all of these structures to damage, and the ED that results is from the cumulative injury of all of these structures [4]. The intimate nature of the prostate and many of these structures underscores how easy it is to incorporate the neurovascular nerve bundle into the most carefully planned radiation field [5]. In addition, there is significant inter-individual variability in the anatomic position of the cavernous nerves that limits the utility of the pretreatment modeling which is performed in an attempt to attenuate this damage [6]. Structures such as the Internal Pudendal Arteries (IPA) also receive radiation from both brachytherapy seeds and EBRT [7]. Damage to the IPA would cause reductions in inflow, and manifest as cavernosal artery insufficiency [8]. Although radiation oncologists take every measure to limit the radiation exposure to the organ of interest, clearly the adjacent tissues have some degree of exposure.

The addition of androgen deprivation treatment (ADT) to radiation regimens compounds the damage to the structures which are critical for erections. ADT is thought to contribute to ED through centrally mediated and penis specific mechanisms [9]. Animal studies have demonstrated a role for testosterone in pathways besides the NO-mediated erection, and testosterone has been implicated in maintaining healthy penile tissue [10]. Traish et al. have neatly summarized the many roles of testosterone in maintaining penile health, including maintaining cavernosal nerve function, producing NO, regulating PDE5, and improving erectile response [11]. In addition to ED, ADT has been associated with decreased libido, gynecomastia, decreased penile and testis size, and likely contributes to changes in ejaculate volume [12]. ADT use not only worsens ED, but it decreases the response of erectile tissue to erectile aids. Teloken et al. investigated 152 patients who received either EBRT or BT; of those men, 35 received a median of 3.8 months of ADT [13]. Comparing the men who did not receive ADT to those that did, the mean erectile function domain score of the International Index of Erectile Function (IIEF) was significantly higher at >24 months after RT (19 ± 7 and 14 ± 4, $p = 0.007$). Even more impressively, fewer men who had received the short course of ADT more 2 years prior were responders to phosphodiesterase-5 inhibitors (PDE5i) (47% vs. 61%, $p = 0.032$). It is unmistakable that ADT has both immediate and long-term effects on sexual function even when it is seemingly "short term."

Brachytherapy

Several aspects unique to brachytherapy need to be considered when reviewing the literature regarding ED outcomes. Although ADT has been shown to have severe side effects, ADT continues to be routinely utilized to shrink the prostate in order to allow a greater condensation of volume covered by the radiation seeds as well as reduce the total radiation dose [14, 15]. In addition, there

are several kinds of isotopes, which can be utilized, such as Iodine 125, Palladium 103, Cesium 131, and Iridium 192; each isotope has widely varied half-lives and different recommended prescription doses. There is very little information regarding the difference in effects that the isotopes may have on ED; however, it should not be assumed that they are interchangeable. This is underscored by the fact that isotope choice can often be based on disease grade so patients receiving certain isotopes may be different at baseline and not broadly applicable to all men undergoing brachytherapy. The number of seeds implanted is dependent on not only the size of the gland, but also on the discretion of the radiation oncologist and physicist planning the dosimetry profile. Number of seeds will have a direct effect on the total amount of radiation that the prostate and surrounding structures receive, and thus the mean dose (Gy) of radiation should always be considered when interpreting publication results.

Although mean radiation dose or biologically effective dose can be used as a proxy for number of pellets used, it should be appreciated that little investigation has been performed on teasing out the role that mechanical placement of various seed numbers might play on outcomes, and whether larger prostates requiring more seeds will have different outcomes than smaller prostates. Radiation dose can also be described as D90 (the dose that 90 % of the prostate received), and conversions between various ways of documenting radiation exposure should be considered. In addition, there is a possible difference between outcomes of permanent seed placements and high-dose-rate temporary implants.

As with any area of medicine, poor study design will cripple the results of any study and diminish their impact. Critical to reporting ED outcomes is establishing baseline EF in order to allow the direct comparison of EF after whatever intervention is being studied. For example, Ong et al. established that 52 % of men at their institution had some complaint of ED prior to receiving brachytherapy [16]. While this rate may not be directly applicable to every population as it was derived from a single institution, it clearly underscores the need for baseline evaluation of ED in order to frame any results that are presented.

ED Outcomes After Brachytherapy

Keyes et al. have recently published one of the largest studies which investigated EF outcomes after brachytherapy [17]. They included 2929 patients who were implanted with Iodine-125 seeds from 1989 to 2012 and had at least 10 months of follow-up; overall median follow-up was 3.5 years and there is no control group (the comparator group was derived using data from the Massachusetts Male Aging Study). The most interesting aspect of their study was the means of assessing erectile function. They, in an unconventional fashion, chose to forego using validated questionnaires such as the IIEF, and instead used a "physician-reported scale" to document patient outcomes based on whether the patient had "unimpaired," "suboptimal erections adequate for intercourse," or "erections inadequate for intercourse." Importantly, the authors state that for many years (they do not provide exact dates) they were not using the suboptimal erection category, and instead all men were dichotomized into inadequate for intercourse or not. The authors, therefore, have clearly biased their results to favor an increased value for "unimpaired" erections despite the fact that they admit to placing patients who clearly had impaired erections into this category. Furthermore, there is also no information regarding frequency of erection, how the physicians queried patients in order to decide on the scale, and whether the answers the patients provided related to their most recent erections, best erections since treatment, natural erections, or erections that were assisted with erectile aids such as PDE5i or penile injections. Keeping these inadequacies in mind, the authors conclude that "more than 80 % of young men have EF preserved 5 years after prostate brachytherapy." It is important to also appreciate that the authors calculated, using data from the MMAS, that 50 % of the ED, which developed within 5 years is attributable to aging, and thus they claim it is not attributable to brachytherapy. This study is being used as an example of why published data are often applicable in a way that allows us to counsel patients, and also because it is one of the largest most recent studies published and will likely be quoted extensively. While the authors

Table 18.1 Recently published erectile function outcomes after brachytherapy

Author	Year	# Patients	Median (range) F/U (months)	Patients who received ADT (%)	Baseline ED incidence (%)	ED incidence after BT (%)
Zuber et al. [21]	2015	134	50 (1–85)	31	NP	91
Pugh et al. [22]	2015	237	25 (1–60)	0	38	44
Ghadjar et al. [23]	2014	31	83 (18–96)	0	35	32
Nishimura et al. [24]	2014	665	60 (NP)	81	42	39–71
Njomnang et al. [25]	2013	241	36 (6–70)	26	45	89
Matsushima et al. [26]	2013	119	12 (NP)	80	87	94
Emara et al. [27]	2012	62	NP (60-NP)	NP	0	37

ED erectile dysfunction, *BT* brachytherapy, *NP* not provided

claim an 80 % EF preservation rate, their methodology is so suspect as to render their conclusions unusable for practical purposes. There is no evidence that their 3-point scale accurately grades erections, but there is evidence that physician querying and reporting of patient's erections is unreliable [18]. Also of note, the median follow-up of this study (3.5 years) is just at the beginning stages of when EF starts to decline following radiation, and does not address the crux of the patient's question: "What will the ultimate effect of brachytherapy be on my EF?" In addition, their 5 year incremental outcomes data are actually extrapolated via statistical modeling and not based directly on patient outcomes.

Ong et al. also present outcomes data for brachytherapy, albeit using a different approach [19]. Three hundred and sixty six patients who underwent permanent seed implant completed the validated IIEF-5 questionnaire at baseline, and 277 (76 %) of men with normal EF were included with a median follow-up of 41 months. These authors also extrapolated data and present results as a 5-year actuarial rate of EF preservation of 59 %. Importantly, the authors demonstrate that 5 % of men pretreatment and 40 % of men post-treatment were using PDE5i. Strictly speaking, "EF preservation" should only be used when looking at EF outcomes for men regarding their baseline erectile function compared to their unaided natural erection post-treatment. If, at baseline, a man does not require erectile aids, then his EF should be described without erectile aids; however, this is not routinely done. Unfortunately, results for men at baseline (without PDE5i) are being compared to the erections that these same men get after treatment while using PDE5i; this is not EF preservation and the data need to be carefully interpreted to identify this fallacy. Crook et al. also present results using the validated IIEF questionnaire for 238 patients who had >5 years of follow-up [20]. The authors admit that they have no information regarding erectile aid usage so their data are lacking this information, but they state that 75 % of those patients had "satisfactory erectile function." Notably, there is no definition for what the authors considered "satisfactory" as that is not how the IIEF is scored. Again, the outcomes data do not provide meaningful answers for patients because of the design of the studies. The definitive study, which defines baseline and post-treatment EF, has appropriate length of follow-up, accounts for erectile aid usage, and clearly delineates the brachytherapy protocol, which was utilized remains to be performed. See Table 18.1 [21–27].

External Beam Radiation

EBRT presents entirely new facets of radiation treatment requiring consideration when interpreting the data. Likely even more so than brachytherapy, there have been dramatic changes in the protocols for EBRT. There are various approaches to EBRT, and these include the conventional four field box technique, three-dimensional conformational radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), stereotactic body radiation therapy (SBRT), and proton beam

radiation therapy (PBRT). Even within these radiation protocols, there is variability between institutions regarding duration, whether radiation is supplied in higher doses over shorter period (hypofractionation) or over a longer course, and the optimal initial and booster doses, which may be given. IMRT, for example, may or may not be image guided, or it may use a variation known as volumetric modulated arc therapy (VMAT). It is unclear to what degree outcomes for institution specific EBRT protocols can be applied to outside institutions because there is the potential for such heterogeneity in approach, and it is unclear what factors are most important for determining EF outcomes. Importantly, margins of radiation will play a role in subsequent sexual function because EBRT may not only be directed at the prostate, but can also be delivered to pelvic lymph nodes and/or the entire pelvis. The field exposed will clearly have ramifications for EF.

Within the EBRT literature there is a debate regarding whether the dose to the penile bulb can be related to risk of ED [28]. It is important to appreciate how RT causes ED, because this understanding will allow appropriate steps to be taken to attenuate the risk. Furthermore, it will also discourage taking steps that do not improve EF but may decrease the oncological efficacy of RT. Rivin et al. demonstrate in a review of the literature that there was a consistent relationship between ED and penile bulb dose, and recommend that the PB receive <50 Gy in order to attenuate the risk of ED after EBRT [29]. Because the bulb (which is merely corpus spongiosum and urethra) contributes almost nothing to erectile rigidity, it is highly unlikely that damage to the bulb plays a role in the development of ED. It is more likely that damage to the adjacent structures, namely the crura of the corpus cavernosum are associated with ED and that the dose to the penile bulb is simply a surrogate for the dose administered to these essential structures. It is more important to consider penile bulb damage in the pathogenesis of urethral strictures that result from exposure to radiation. It is reasonable to document crural exposure to radiation because studies have shown that the crura can contribute to the pathophysiology of ED after EBRT. Mulhall et al. performed dynamic infusion cavernosometry and cavernosography on 16 men with functional erections who underwent radiation with a mean follow-up of 11 months [8]. These authors demonstrated that 80 % of their subjects had venous leak, and the majority had leak from their crura.

As with brachytherapy, studies of EBRT need to clearly explain what, if any, ADT was used in conjunction with EBRT and what the duration was. There is evidence, however, that ADT could improve cancer-specific outcomes, so the risk to a well-informed patient is more easily justified [30]. The duration of follow-up is also a prominent issue with EBRT outcomes studies, as so many studies have median follow-ups that are frankly too abbreviated to determine what the actual EF outcome will eventually be for patients. Furthermore, the rapid evolution of new radiation modalities and protocols means that no long-term studies have even reached maturity to allow them to be performed.

ED Outcomes After EBRT

Resnick et al. published the outcomes of 491 men who received EBRT in 1994–1995 for prostate cancer using a self-administered questionnaire that had multiple domains, including sexual function [31]. These authors demonstrate that 71.9 % of men stated that they had erections insufficient for intercourse at 5 years post-treatment; this increased to 93.9 % at 15 years after treatment. Although this demonstrates a significant ED rate after EBRT, it is again unclear what effect erectile aids might have attenuating these numbers. Because it was a cohort study, no information regarding the details of the EBRT are available, and so no information can be ascertained regarding whether the 1994–1995 radiation protocols apply to modern EBRT.

Siegel et al. queried a single institution's database for patient who underwent EBRT before 1998, and 319 men identified had physician reported erectile function before and after treatment [32]. Prior to treatment, 38.9 % of patients

Table 18.2 Recently published erectile function outcomes after external beam radiation therapy

Author	Year	# Patients	Median (range) F/U (months)	Patients who received ADT (%)	Baseline ED incidence (%)	ED incidence after EBRT (%)
Resnick et al. [31]	2013	491	NP (NP-180)	NP	NP	94
Obayomi-Davies et al. [34]	2013	97	NP (NP-24)	0	0	46–49
Spratt et al. [35]	2013	427	NP	NP	0	74
Magli et al. [36]	2012	19	NP	0	0	58–100
Haugnes et al. [37]	2012	158	35 (17–64)	NP	NP	70

EBRT external beam radiation therapy

were defined as having erections consistently inadequate for penetration, and at a median follow-up of 51 months, 85.4 % of men were described as having erections insufficient for penetration. Brown et al. found that at a median follow-up of 36.8 months after IMRT, 75 % of men who completed the IIEF-5 had some degree of ED [33]. Because SBRT is relatively new, there are no long-term studies that clearly define outcomes. Obayomi-Davies et al. demonstrated that at 24 months after treatment with SBRT, only 54.4 % percent of men had erections hard enough for intercourse with or without erectile aids [34]. See Table 18.2 [31, 34–37].

Androgen Deprivation Therapy

Although "ADT" is typically considered as one entity because the oncologic outcome is the same, it is actually an umbrella term encompassing several medical or surgical means of abolishing or decreasing androgen effect. Surgical castration, for example, will leave the adrenal glands intact, and thus those men will maintain adrenal androgen production while having an absolute loss of testicular hormone production. Alternatively, androgen production can be significantly decreased or androgen receptors can be blocked; in the former, the decrease is not absolute, and in the latter, it is possible to actually increase the amount of circulating dihydrotestosterone and testosterone (and thus increasing the conversion of androgens to estrogens). Potosky et al. demonstrated significantly worse gynecomastia in men who received luteinizing hormone-releasing hormone than those men who underwent orchiectomy (24.9 % vs. 9.7 %, $p<0.01$) [38]. Readers should therefore keep in mind that there are many ways to achieve androgen deprivation, and there are likely differences in sexual dysfunction outcomes that stem directly from which androgen deprivation method is chosen. Similarly, the duration of ADT varies significantly. Surgical castration is permanent, for example, but NADT can occur over a variety of months, intermittently or continuously.

ED Outcomes After ADT

Daly et al. used physician directed questions to query EF in men who received either 4 or 8 months of neoadjuvant ADT (NADT) prior to EBRT [39]. These authors, despite foregoing a validated questionnaire and instead relying on physician interpretation of patient answers, show that the calculated probability of EF preservation at 5 years was only 28 and 24 % in the 4 and 8 month NADT groups, respectively. Schover reviewed the sexual dysfunction sequelae of men on ADT, and found that EF does not recover in half of men who underwent ADT even after the treatment has been stopped [40].

Conclusions

Despite the decades that have been spent treating prostate cancer patients with radiation to the pelvis, very little progress has been made clearly elucidating the sexual function sequelae that men and their partners face. It is plausible that the vast majority of men who undergo any type of radia-

tion will have ED 5 years after their treatment. Future studies need to incorporate solid methodologies in order to provide results that are meaningful to patients and the health care providers who seek to counsel them.

References

1. 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;49:822–30.
2. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999;11:319–26.
3. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am. 2005;32:379–95. v.
4. Goldstein I, Feldman MI, Deckers PJ, Babayan RK, Krane RJ. Radiation-associated impotence. A clinical study of its mechanism. JAMA. 1984;251:903–10.
5. McLaughlin PW, Troyer S, Berri S, et al. Functional anatomy of the prostate: implications for treatment planning. Int J Radiat Oncol Biol Phys. 2005;63:479–91.
6. Takenaka A, Murakami G, Matsubara A, Han SH, Fujisawa M. Variation in course of cavernous nerve with special reference to details of topographic relationships near prostatic apex: histologic study using male cadavers. Urology. 2005;65:136–42.
7. McLaughlin PW, Narayana V, Meirovitz A, et al. Vessel-sparing prostate radiotherapy: dose limitation to critical erectile vascular structures (internal pudendal artery and corpus cavernosum) defined by MRI. Int J Radiat Oncol Biol Phys. 2005;61:20–31.
8. Mulhall J, Ahmed A, Parker M, Mohideen N. The hemodynamics of erectile dysfunction following external beam radiation for prostate cancer. J Sex Med. 2005;2:432–7.
9. Trost LW, Serefoglu E, Gokce A, Linder BJ, Sartor AO, Hellstrom WJ. Androgen deprivation therapy impact on quality of life and cardiovascular health, monitoring therapeutic replacement. J Sex Med. 2013;10 Suppl 1:84–101.
10. Reilly CM, Lewis RW, Stopper VS, Mills TM. Androgenic maintenance of the rat erectile response via a non-nitric-oxide-dependent pathway. J Androl. 1997;18:588–94.
11. Traish AM, Goldstein I, Kim NN. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. Eur Urol. 2007;52:54–70.
12. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67:825–36.
13. Teloken PE, Ohebshalom M, Mohideen N, Mulhall JP. Analysis of the impact of androgen deprivation therapy on sildenafil citrate response following radiation therapy for prostate cancer. J Urol. 2007;178:2521–5.
14. Isbarn H, Boccon-Gibod L, Carroll PR, et al. Androgen deprivation therapy for the treatment of prostate cancer: consider both benefits and risks. Eur Urol. 2009;55:62–75.
15. Lee WR. The role of androgen deprivation therapy combined with prostate brachytherapy. Urology. 2002;60:39–44. discussion.
16. Ong WL, McLachlan H, Millar JL. Prevalence of baseline erectile dysfunction (ED) in an Australian cohort of men with localized prostate cancer. J Sex Med. 2015;12:1267–74.
17. Keyes M, Pickles T, Crook J, et al. Effect of aging and long-term erectile function after iodine-125 prostate brachytherapy. Brachytherapy. 2015;14:334–41.
18. Mulhall JP. Re: return of erections and urinary continence following nerve sparing radical retropubic prostatectomy. J Urol. 1994;152:1213–4.
19. Ong WL, Hindson BR, Beaufort C, Pharoah P, Millar JL. Long-term erectile function following permanent seed brachytherapy treatment for localized prostate cancer. Radiother Oncol. 2014;112:72–6.
20. Crook J, Borg J, Evans A, et al. 10-year experience with I-125 prostate brachytherapy at the Princess Margaret Hospital: results for 1,100 patients. Int J Radiat Oncol Biol Phys. 2011;80:1323–9.
21. Zuber S, Weiss S, Baaske D, et al. Iodine-125 seed brachytherapy for early stage prostate cancer: a single-institution review. Radiat Oncol. 2015;10:49.
22. Pugh TJ, Mahmood U, Swanson DA, et al. Sexual potency preservation and quality of life after prostate brachytherapy and low-dose tadalafil. Brachytherapy. 2015;14:160–5.
23. Ghadjar P, Oesch SL, Rentsch CA, et al. Late toxicity and five year outcomes after high-dose-rate brachytherapy as a monotherapy for localized prostate cancer. Radiat Oncol. 2014;9:122.
24. Nishimura S, Yorozu A, Ohashi T, et al. Five-year potency preservation after iodine-125 prostate brachytherapy. Int J Clin Oncol. 2014;19:940–5.
25. Njomnang Soh P, Delaunay B, Thoulouzan M, et al. Erectile function after permanent 125I prostate brachytherapy for localized prostate cancer. Basic Clin Androl. 2013;23:2.
26. Matsushima M, Kikuchi E, Maeda T, et al. A prospective longitudinal survey of erectile dysfunction in patients with localized prostate cancer treated with permanent prostate brachytherapy. J Urol. 2013;189:1014–8.
27. Emara AM, Chadwick E, Nobes JP, Abdelbaky AM, Laing RW, Langley SE. Long-term toxicity and quality of life up to 10 years after low-dose rate

brachytherapy for prostate cancer. BJU Int. 2012; 109:994–1000.
28. Roach 3rd M, Nam J, Gagliardi G, El Naqa I, Deasy JO, Marks LB. Radiation dose-volume effects and the penile bulb. Int J Radiat Oncol Biol Phys. 2010;76:S130–4.
29. Rivin del Campo E, Thomas K, Weinberg V, Roach 3rd M. Erectile dysfunction after radiotherapy for prostate cancer: a model assessing the conflicting literature on dose-volume effects. Int J Impot Res. 2013;25:161–5.
30. Pagliarulo V, Bracarda S, Eisenberger MA, et al. Contemporary role of androgen deprivation therapy for prostate cancer. Eur Urol. 2012;61:11–25.
31. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368:436–45.
32. Siegel T, Moul JW, Spevak M, Alvord WG, Costabile RA. The development of erectile dysfunction in men treated for prostate cancer. J Urol. 2001;165:430–5.
33. Brown MW, Brooks JP, Albert PS, Poggi MM. An analysis of erectile function after intensity modulated radiation therapy for localized prostate carcinoma. Prostate Cancer Prostatic Dis. 2007;10:189–93.
34. Obayomi-Davies O, Chen LN, Bhagat A, et al. Potency preservation following stereotactic body radiation therapy for prostate cancer. Radiat Oncol. 2013;8:256.
35. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2013;85:686–92.
36. Magli A, Giangreco M, Crespi M, et al. Erectile dysfunction after prostate three-dimensional conformal radiation therapy. Correlation with the dose to the penile bulb. Strahlenther Onkol. 2012;188:997–1002.
37. Haugnes HS, Melby B, Larsen KM, Langdal I, Rasi M, Bremnes RM. Assessment of late urinary, bowel and sexual function after dose escalation from 70 to 76 Gy using image-guided radiotherapy in curative treatment of prostate cancer. Scand J Urol Nephrol. 2012;46:124–32.
38. Potosky AL, Knopf K, Clegg LX, et al. Quality-of-life outcomes after primary androgen deprivation therapy: results from the prostate cancer outcomes study. J Clin Oncol. 2001;19:3750–7.
39. Daly PE, Dunne MT, O'Shea CM, Finn MA, Armstrong JG. The effect of short term neo-adjuvant androgen deprivation on erectile function in patients treated with external beam radiotherapy for localised prostate cancer: an analysis of the 4- versus 8-month randomised trial (Irish Clinical Oncology Research Group 97-01). Radiother Oncol. 2012;104:96–102.
40. Schover LR. Sexual healing in patients with prostate cancer on hormone therapy. Am Soc Clin Oncol Educ Book. 2015;35:e562–6.

Penile Length: Natural History, Preservation, and Recovery

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Introduction

Penile size has been associated with virility and strength for millennia. Across different cultures, there have been various penile enhancement strategies dating back to ancient times. The sadhus of India and the Cholomec tribe in Peru utilized hung weights to increase their penile lengths [1]. The Topinama tribe of Brazil in the sixteenth century allowed poisonous snakes to bite their penises in an attempt to enlarge them via swelling [2]. It is relatively common, even today, for men to use medically questionable or unproven methods, such as injection of exogenous substances or implants of foreign bodies under their genital skin, in an attempt to increase penile length or girth.

The perception of having a large penis has been associated with significantly higher self-esteem in men [3]. Interestingly, a survey of over 52,000 subjects showed 85 % of women were satisfied with their partner's penis size, while only 55 % of the men were satisfied with their own penis size [3]. An extreme manifestation of penile length obsession has been defined by the *Diagnostic and Statistical Manual of Mental Disorders* as genital retraction syndrome [4, 5]. Men with this genital retraction syndrome have an unshakable belief that their genitals are retracting and will eventually disappear; the condition is characterized by an absence of actual measurable genital changes [5].

It has never been shown that penile length is associated with the two primary purposes of the penis: procreation and urination. Clearly, however, penile length is a profound factor in psychological health for many men. It is therefore essential to appreciate and recognize the effects that certain urological diseases and therapies can have on penile size in order to appropriately manage and counsel patients.

Measurement of Penile Length and Curvature

The majority of penile growth occurs mainly between two periods of development. The first rapid rate of growth is seen between infancy and the age of 5. The second significant growth period occurs between the onset of puberty and approximately 17 years of age [6]. For the purposes of this chapter, we focus exclusively on adult penile size.

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There have been numerous described methods utilized to objectively assess stretched flaccid penile length. It should be noted that, with any measurement modality, level of arousal and room temperature can cause variation in penile length for a given patient. Measurements are typically performed with flaccid penis status. Partial or full erection during measurement should be noted and a flaccid measurement should be obtained at a later time. Cold temperature and recent ejaculation are other factors that can affect penile dimensions [7]. Most studies define stretched flaccid penile length as the linear distance along the dorsal side of the penis extending from the pubopenile skin junction to the tip of the glans with the penile circumference being measured at the middle of the shaft. [7–9]

The glans penis should be held on gentle traction with the patient in the supine position, with the observer's other hand holding a ruler that is placed at the penis base and along the dorsal aspect of the shaft. Measurements in medical practice are usually reported in millimeters or centimeters, not inches. Simple plastic rulers are ideal for such measurements and should be fully wiped clean by antiseptic solution between uses. Commercially available disposable penile measurement rulers are also available (UroSciences, Inc., Jericho, NY). Several studies have reported average penile sizes. In a recent analysis of previous studies that pooled average penile sizes for over 15,000 men, it was found that the average penile length in the flaccid, stretched flaccid, and erect states was 9.16, 13.24, and 12.12 cm, respectively [7]. The average flaccid and erect circumference measurement at mid-shaft was 9.31 and 11.66 cm, respectively [7].

Another important measurement of the human penis is an assessment of any curvature or penile deformity. Accurate measurement is important for determining optimal management options, assessment of changes following treatment, and for research purposes. Penile curvature can be measured using at-home photography, the vacuum erection device (VED), or with intracavernosal injection (ICI) and goniometer in the physician's office. Ohebshalom et al. [10] showed that the most accurate way and gold standard method in measuring any penile curvature/deformity is by using intracavernosal injections of vasoactive agents to induce an artificial erection and then utilizing a goniometer to measure the degree of curvature/deformity. Further, relying on patient self-assessment of curvature in order to document deformity magnitude has been shown to be insufficient, given the poor correlation between subjective self-assessment and objective physician measurement of curvature [11].

Erectile Dysfunction

Erectile dysfunction (ED) is defined as the inability to develop or maintain an erection suitable for sexual performance. The Massachusetts Male Aging Study demonstrated the overall prevalence of ED in USA to be 52 % among men aged 40–70 years, with increasing prevalence in older age. At age 40, approximately 40 % of men are affected. The rate increases to almost 70 % by age 70 [12]. The National Institutes of Health (NIH) has estimated that approximately 30 million men in the USA suffer from ED [13].

For men with ED refractory to medication, insertion of an inflatable penile prosthesis (IPP) represents the standard of care. It is crucial to be able to set realistic expectations for the patient as the overall outcome of penile prosthesis implantation is largely dependent on patient and partner satisfaction, but this task is made more challenging by conflicting data. A recent study showed that, following IPP surgery, 70 % of men had a measurable loss in penile length compared with preoperative measurement of stretched flaccid length, while only 43 % reported a subjective assessment of shortening [14].

Pharmacologically induced erect penile length and stretched penile length are both good predictors of post-inflatable prosthesis penile length [14]. In contradistinction, Deveci et al. [15] found that 72 % of men subjectively reported length loss following IPP, but overall there was no significant measurable decrease in size. We feel that it is helpful to preoperatively counsel patients

that there will definitely not be an increase in penile length, as many expect, and that they should only proceed if they are willing to accept a potential loss of length.

There are multiple potential reasons why patients may have perceived or experienced actual penile length loss following IPP surgery. First, men who are candidates for IPP typically have not had rigid erections for a prolonged period of time. In the intervening time period between good natural erections and IPP surgery, they may have developed corporal fibrosis or scarring that limits the elasticity of the tunica albuginea. The decreased length due to fibrosis may not be apparent until the IPP restores rigid erections, sometimes for the first time in years. Second, penile prostheses also do not provide glanular engorgement, as is experienced with natural erections. This lack of glanular engorgement may contribute to the perception of a decreased penile size. Third, men who undergo IPP surgery are typically older and have suffered from ED for many months or years. Their recollection of their true penile sizes prior to developing ED may be inaccurate. Finally, as men age, they may develop pannus fat that can give the appearance of a partially buried (i.e., smaller) penis.

Peyronie's Disease

Peyronie's disease (PD) is characterized by the development and accumulation of collagen in the tunica albuginea of the corpora cavernosa. PD is associated with penile nodular induration, ED, penile curvature, painful erections, and loss of penile girth and length [16]. Up to a third of patients with progressive PD will experience penile shortening [17]. PD is estimated to affect approximately 3–9 % of men [18]. Quality of life may be affected and may result in depression, lower self esteem, and fear of sexual activity [19].

PD can be characterized by two phases. The first phase is the acute inflammatory phase which is characterized by the development of a painful and evolving plaque and progression of penile curvature. This phase typically lasts 6–18 months. The acute phase is followed by the chronic phase, during which the plaques are no longer associated with pain and deformity stabilizes. Treatment options available for PD include observation, oral pharmacotherapy, intralesional injection therapy, and surgical management. The goal of PD treatment is to correct any penile deformity while preserving penile length and the ability to accomplish and maintain an erection adequate for sexual intercourse [20, 21].

Observation is an appropriate management option for men with PD with satisfactory erectile function and mild penile curvature which does not prevent successful penetration in sexual intercourse. Oral therapies for PD include pentoxifylline (PTX), potassium para-aminobenzoate, colchicines, tamoxifen citrate, acetyl-L-carnitine, and vitamin E. The most commonly used oral therapy is vitamin E, despite the fact that no placebo-controlled trials have demonstrated any clinical benefit or shown any superiority of vitamin E versus placebo as a treatment for PD. [22–25]

Since no oral therapy has been shown to consistently and reliably reduce penile deformity in PD in a clinically meaningful way, many practitioners recommend injection treatments of penile plaques. Intralesional drug injections are generally safe and well-tolerated. There are currently three intralesional drug treatments that have shown to be efficacious in the treatment of PD: verapamil, interferons, and collagenase.

Verapamil is a calcium channel blocker that affects fibroblast metabolism by increasing collagenase activity and decreasing collagen production [26, 27]. Several studies have demonstrated that intralesional verapamil (ILV) for PD significantly improved plaque size, plaque-associated penile narrowing, penile curvature, and erectile function [28–30]. These studies include a prospective non-randomized trial of 140 patients with a mean duration of PD of 17.7 months. After 12 treatment sessions, 121 patients underwent penile deformity assessment with ICI (used as part of a penile duplex Doppler ultrasound). The authors found that penile curvature decreased in 73 patients (60 %, mean decrease in curvature

from baseline of 30°), increased in 10 (8 %, mean increase of 26°), and remained unchanged in 38 (31 %) [29]. In contrast to these findings, Shirazi et al. [31] performed a randomized, single-blind, placebo-controlled trial in 2009 comparing ILV with injected saline; the results showed an absence of significant differences or improvements in penile deformity between the two groups.

Another intralesional therapy available for the treatment of PD is collagenase, which is an enzyme that acts to lyse the collagen deposits found in PD plaques. Gelbard et al. [32] conducted a recent phase IIb study of the clinical efficacy of intralesional collagenase. A total of 147 patients were randomized into four groups to receive collagenase or placebo, with or without penile modeling. Each treatment cycle included two injections within 48 h of each other followed by penile modeling by a physician within 72 h and subsequent home modeling three times daily. The modeling consisted of gradual stretching of the flaccid penis in the opposite direction of the curvature. There was statistically significant improvement in penile curvature in the collagenase group compared to placebo group (29 % vs. 11 %, $p = 0.001$) as well as in the modeling group compared to the placebo group [32]. Finally, in 2013, Gelbard et al. [33] conducted two separate phase III multicenter, randomized, double-blind, placebo-controlled trials to assess the clinical efficacy and safety of intralesional collagenase. They found a statistically significant improvement in penile curvature deformity and symptom bother in the treated group compared to the placebo group. However, none of these studies showed a statistically significant change in the subjective assessment of penile length among patients treated with intralesional collagenase, although penile length changes were not measured objectively and were not the primary endpoints of these studies. Nonetheless, based on these studies, intralesional collagenase became the first drug to be approved by the US Food and Drug Administration for the treatment of Peyronie's disease.

Penile traction therapy is a controversial modality for treating PD and, generally, penile length loss issues. Levine et al. [34] published the first study on traction therapy for PD; the authors demonstrated an average reduction in penile curvature of 33 % and an increase in erectile function in patients treated with traction therapy for 2–8 h daily over 6 months. They also found that stretched penile length increased in all patients. Increased penile length measurements ranged from 0.5 to 2.0 cm; erect diametric girth increases of 0.5–1.0 cm were also recorded. The reasons for these changes have not been clearly elucidated.

Gontero et al. [35] evaluated 15 patients who underwent traction therapy using the Andropenis (Andromedical, Madrid, Spain) penile extender for 5–9 h per day over 6 months. They showed that mean stretched and flaccid penile length increased by 1.3 and 0.83 cm, respectively, at 6 months. Although the patients had minimal reduction in curvature, they generally rated themselves as satisfied with the treatment outcome. The authors hypothesized that increased penile length is responsible for patient satisfaction. Although data remain scant, traction devices hold promise for increasing penile length in men with PD. This concept is reflected in the International Consultation of Sexual Medicine guidelines that state, "early evidence from two small non-controlled prospective trials have reported a reduction in deformity and increased penile length with traction therapy" [36].

Surgical treatment of PD should be considered in patients who have failed medical therapy or in those who desire definitive treatment. Common indications for surgical treatment of PD include stable deformity with pain-free erections for at least 3 months, extensive plaque calcifications, deformity that precludes sexual intercourse, and failed non-surgical treatment [20, 37]. Surgical options for PD include penile plication, plaque incision/excision and graft, and IPP surgery with or without modeling, plication, or incision/grafting techniques. Choice of surgical treatment is individualized to the patient based on factors including degree and nature of deformity, degree of erectile function, and penile length.

For men with PD with normal erectile function, penile length adequate for sexual intercourse,

uniplanar penile curvature less than 60°, and absence of hourglass deformity or hinge, the most appropriate surgical option is a plication procedure [36, 38]. Complete curvature correction rates following plication procedures range from 42 to 100 % with overall satisfaction ranges from 68 to 100 % [39–42]. Plication procedures are also known as shortening procedures. To estimate penile length after plication surgery, a string should be held against the concave edge of the curved erect penis preoperatively. The concave side is always shorter than the opposite convex side. Plication essentially shortens the convex side so that it matches the shortened side in length—in this manner the curvature effect is removed. Besides shortening, which is expected by definition, the most common complications of penile plication procedures include persistent pain, persistence or recurrence of penile curvature, penile hematoma, urethral injury, and loss of sensation. Results from multiple studies are summarized in Table 19.1.

Another surgical modality to treat PD is plaque incision, or excision with graft, procedures. These are also described as tunical lengthening procedures. They are most appropriate for patients with excellent preoperative rigidity (since postoperative impairment of erectile function is common), complex penile deformity, curvature greater than 60° in magnitude, large plaques, destabilizing hourglass or hinge effect, and short penile length [20, 43, 44]. During plaque incision and grafting procedures, an incision of the plaque is made at the point of maximum curvature on the convex side of the penis. Subsequently, graft material is used to repair the defect and lengthen the penis [44–46]. During a plaque excision and grafting procedure, the plaque is partially or completely surgically excised. The calcified area of tunica is then replaced with a graft. A partial plaque excision should be performed rather than a total plaque excision in hopes of decreasing the risk of irreversible erectile tissue damage and permanent postoperative ED [47].

A variety of graft materials that can be used for such procedures: autologous grafts, allografts, xenografts, and synthetic grafts [20, 43]. The ideal graft is one that is similar to normal tunica albuginea in strength and elasticity, has minimal tissue reaction, is readily available, easy to suture, inexpensive, resistant to infection, and able to preserve erectile capacity [37, 48]. Autologous tissues used for grafting include saphenous vein, rectus fascia, tunica vaginalis, dermis, and buccal mucosa. Allograft or xenograft material include cadaveric or bovine pericardium [49] and porcine small intestinal submucosa [50, 51]. Synthetic grafts include polytetrafluoroethylene. Synthetic grafts are not typically recommended to be used for management of PD due to the risks of local inflammation, infection, and fibrosis [52].

One of the most concerning risks of such procedures is postoperative ED. Research has shown that certain variables that be predictors of postoperative ED including preoperative ED, age of the patient (>55 years), evidence of corporal veno-occlusive dysfunction on duplex ultrasound analysis, ventral curvature, and the severity of curvature. Other complications following a plaque incision/excision with graft procedure includes infection, fibrosis, decreased penile sensation from disruption of sensory nerves, hematoma, and penile shortening from graft contraction [44, 53, 54]. Published surgical outcomes for various plaque incision and excision with graft procedures are summarized in Table 19.2.

For men with PD curvature and ED, or profound penile instability in PD (even if erectile function is otherwise adequate), IPP surgery is frequently recommended [43, 55, 56]. In the setting of IPP surgery, adjunctive procedures to help straighten the penis include modeling [57], plication [58], plaque-releasing incision with or without a graft [43, 55], and the surgical "scratch" technique. [59] Outcomes related to these procedures are summarized in Table 19.3.

Radical Prostatectomy

Prostate cancer is the most common non-skin cancer and the second leading cause of cancer-related death in men in the USA. The American Cancer Society estimates that, in 2015, approximately 220,800 new cases of prostate cancer will

Table 19.1 Penile plication procedures

			Surgical outcomes (%)						
Procedure	Author/date	Patients (N)	Mean follow-up (mos)	Straightening	Shortening	Postoperative ED	Sensory change	Pain	Satisfaction
Tunica albuginea plication (TAP	Paez et al. 2007 [41]	76.0	70.5	42.1	NR	60.5	65.8	27.6	NR
	Taylor et al. 2008 [98]	61.0	72.0	93.0	18.0	10.0	31.0	NR	84.0
Nesbit	Syel et al. 2003 [46]	57.0	84.0	61.9	50.0	12.2	21.4	NR	76.2
Yachia Procedure	Daitch et al. 1999 [99]	19.0	24.1	93.0	57.0	7.1	0.0	0.0	79.0
	Rehman et al. 1997 [100]	26.0	22	73.1	73.1	23.1	19.2	NR	77.0
16- or 24-dot Procedure	Gholami et al. 2002 [101]	132.0	6.0 to 30.0 (range)	93.0	41.0	NR	6.0	11.0	96.0
Penoscrotal Plication	Dugi et al. 2010 [102]	48.0	4.0 to 6.0 weeks	93.0	0.0	NR	0.0	6.0	93.0
Tunical Plication Combined with Plaque Thinning	Ding et al. 2010 [39]	18.0	50.5	83.3	66.7	0.0	NR	NR	100.0

NR Not Reported

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Table 19.2 Graft materials used in Peyronie's disease reconstructive surgery and surgical outcomes

				Surgical outcomes (%)					
Procedure/graft	Author/date	Patients (N)	Mean follow-up (mos)	Straightening	Shortening	Postoperative Ed	Sensory change	Pain	Satisfaction
Dermal graft	Chung et al. 2010 [103]	6	101.8	50.0	17.0	Signficantly lower than preoperative ED ($p<0.01$)	13.0	NR	35.0
Tutoplast[a]		23	79.2	87.0	17.0		NR	NR	NR
Small intestinal mucosa (SIS)		17	75.5	76.6	29.0		NR	NR	NR
Cadaveric pericardial Graft	Levine et al. 2003 [56]	40	22.0	98.0	33.0	30.0	2.0	NR	NR
Dermal flap	Simonato et al. 2010 [104]	22	95.0	63.6	NR	31.8	NR	NR	40.9
TachoSil[b]	Horstmann et al. 2011 [40]	43	63.0	84.0	93.0	2.3 out of 4 (EHS)	16.0	7.0	51.0
Buccal mucosa	Cormio et al. 2009 [105]	15	13.1	100.0	0.0	0.0	0.0	NR	93.3
Venous patch	El-Sakka et al. 1998 [106]	112	18.0	96.0	17.0	12.0	10.0	6.2	92.0
Human pericardial	Taylor et al. 2008 [98]	81	58.0	91.0	33.0	32.0	31.0	NR	75.0
Rectus sheath	Craatz et al. 2006 [107]	12	4 to 10	100.0	NR	0.0	NR	NR	58.3
Tunica vaginalis	O'Donnell et al. [108]	25	42.2	88.0	96.0	68.0	16.0	NR	NR
Dermal graft	Goyal et al. 2008 [109]	11	6 to 24	81.8	NR	9.1	18.2	0.0	81.8
Porcine 4-layer SIS	Knoll et al. 2007 [51]	162	38.0	91.0	5.0	21.0	17.0	0.0	NR

ED Erectile dysfunction; *NR* Not reported; *EHS* Erection hardness score

[a]Tutoplast® is a commercially available, modified human fascia lata that can act as a scaffold to allow tunical regeneration (Tutoplast®, Mentor Corp, Santa Barbara, CA, USA) [62]

[b]TachoSil® (surgical patch) combines the bioactive mechanism of action of human coagulation factors, fibrinogen and thrombin, with the mechanical support of a [equine] collagen patch (Takeda Pharmaceuticals International GmbH, Zurich, Switzerland) [52]

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Table 19.3 Penile prosthesis implantation

			Surgical outcomes (%)						
Procedure	Author/date	Patients (N)	Mean follow-up (mos)	Straightening	Shortening	Postoperative ED	Sensory change	Pain	Satisfaction
Inflatable Penile Prosthetic Implantation	Levine et al. 2010 [110]	90	49.0	4.0	3.0	NR	2.0	NR	84.0
	Levine et al. 2000 [55]	46	39.0	100.0	7.0	0.0	9.0	NR	NR
Soft, Silicon, Axially Resistant, Prosthetic	Austoni et al. 2005 [111]	80	113.0	100.0	NR	0.0	5.0	7.5	95.0
Silicon Soft Dynamic Antiextrusion Prosthetic Implantation	Grasso et al. 2008 [112]	12	72.0	100.0	NR	100.0	NR	NR	91.0
Transcorporeal Incision (TCI)	Shaeer et al. 2010 [113]	16	14.0	100.0	NR	100.0	0.0	NR	100.0

ED Erectile Dysfunction, *NR* Not Reported

be diagnosed in the USA and nearly 27,540 men will die from the disease. Approximately 1 man in 7 will be diagnosed with prostate cancer during his lifetime.

One of the more prevalent modalities utilized today to treat prostate cancer is radical prostatectomy (RP). Although often successful in treating prostate cancer, risks of RP surgery include infection, bleeding, urinary incontinence, ED, and penile shortening. Parekh et al. [60] found that a perceived reduction in penile size post-RP was significantly associated with disruption of close emotional relationships and increased treatment regret. Penile length changes after RP have been well recognized (Table 19.4).

Fraiman et al. [61] found significant decrease in all penile dimensions after RP, including decreased penile length and decreased volume in the flaccid and erect states, with the most substantial change occurring between the first 4 and 8 months postoperatively. Munding et al. [62] found that 71 % of men had a significantly shorter penis after RP, with 48 % of them experiencing greater than 1 cm decrease in penile length. Savoie et al. [63] found similar results in their cohort of patients with 68 % of patient having a decrease in the stretched penile length 3 months postoperatively.

Engel et al. [64] studied penile length after robot-assisted RP and found a median penile shortening of 0.64 cm 1 month postoperatively. Interestingly, however, they found that penile length had returned to the preoperative measurement 9 months postoperatively. This may be explained by the fact that the parasympathetic nervous signaling to the penis (that cause tumescence), mediated by the cavernous nerves, is normally in a state of dynamic balance against the sympathetic nerves that richly innervate the cavernosa (and cause detumescence) [65–67]. During RP the cavernous nerves are frequently injured, and the unopposed sympathetic action may be a major factor that contributes to the exaggerated state of detumescence in the early postoperative period [66]. Over time, it is thought that the cavernous nerves often recovery to some degree [68], which may account for the study's findings. Consistent with the concept of shortening due to unopposed sympathetic penile innervation, post-RP penile length shortening has been shown to be independently associated with postoperative erectile function outcome and nerve preservation status [69]. Carlsson et al. [70] found that extensive nerve-sparing surgical technique was associated with less self-perceived penile shortening, actual penile lengths were not measured in their study. However, Briganti et al. [71] found no difference between preoperative and postoperative values for penile length and girth in the erect and flaccid states in men who underwent bilateral nerve-sparing RP.

A competing etiologic theory to explain penile shortening following RP has been suggested: removal of the prostate and surgical attachment of the bladder neck directly to the pendulous urethra causes shortening because of removal of a length of prostatic urethra that previously intervened between the newly anastomosed segments. However, the prostatic urethra length does not relate to measured penile length. Furthermore, the bladder neck is brought down to the penile urethra; the penile urethra is not mobilized towards the bladder.

Another possible mechanism for longer term penile shortening following RP relates to the development of penile fibrosis secondary to a prolonged, profound period of ED. ED following RP occurs, as noted previously, due to damage to the neurovascular mechanism responsible for initiating erections. Even with bilateral nerve-sparing RP, mild neuropraxia can cause ED that lasts as long as 9–12 months [66]. During this period of neuropraxia, nocturnal erections are absent or diminished, leading to a state of persistent penile hypoxia [66].

Penile hypoxia has been one the most important precipitating factors in the formation of cavernosal fibrosis. Nocturnal erections have been implicated in preserving normal erectile function by preserving normal erectile function by providing regular tissue oxygenation [72]. Therefore, it has been postulated that the lack of early postoperative nocturnal erections results in a decreased amount of regular tissue oxygenation and ultimately the development of fibrosis [72]. Iacono et al. [73] performed corporal cav-

Table 19.4 Penile length changes after radical prostatectomy

Author	Year	No. of patients	Time interval	Main outcomes
Carlsson [70]	2012	1411	24.2 months	55 % of patients reported self-perceived penile shortening
Engel [64]	2011	127	11 months	0.64 cm shortening at 1 month No decrease in length observed at 9 months or beyond.
Gontero [69]	2007	126	1 year	1.34 cm shortening—flaccid length 2.30 cm shortening—stretched length
Briganti [71]	2007	33	6 months	No statistically significant length changes, both flaccid and erect states
Savoie [63]	2003	63	3 months	19 % had 15 % shortening—stretched length 1.2 cm shortening—flaccid length 1.1 cm shortening—stretched length
Munding [62]	2001	31	3 months	13 % increased stretched length 16 % no change in stretched length 71 % had decreased length: 23 %—up to 0.5 cm 35 %—1.0–2.0 cm 13 %—>2.0 cm
Fraiman [61]	1999	100	1.7–27.6 months	8 % decrease in flaccid length 9 % decrease in erect length Greatest change at 4–8 months

ernosal biopsies before RP, as well as 2 and 12 months postoperatively. Compared with preoperative biopsies, there was a progressive increase in disorganized collagen content at the 2 and 12 postoperative periods, with corresponding decrease in elastic smooth muscle bundles [73]. Mulhall [74] showed an increased rate of PD development that became apparent in post-RP men who were undergoing initial ICI treatment for ED. Cavernous nerve injury has also been shown to result in apoptosis of corporal smooth muscle [75, 76] and sympathetic hyperinnervation [26, 77].

It is important to note that penile shortening is not solely limited to surgical treatments of prostate cancer. This was shown by Hall et al. [78] who looked at penile length changes in men treated with a combination of androgen suppression and radiation therapy. They found that there was a statistically significant decrease in penile length in men treated with hormonal suppression plus radiation. Although data are limited, there is also evidence that external beam radiation can lead to penile fibrosis and ultimately penile shortening [78]. Furthermore, loss of penile volume and length is common for men undergoing androgen ablation [78].

Penile rehabilitation is an important strategy in post-prostatectomy patients to help mitigate penile length loss. Penile rehabilitation encourages artificial induction of erections after surgery to facilitate tissue oxygenation, reduce cavernosal fibrosis, and increase the likelihood of preserving erectile function [79]. Vacuum erection devices (VED) use negative pressure to distend the corporal sinusoids and to increase blood inflow into the penis, which causes passive penile engorgement [79]. It has also been suggested that use of VEDs can help inhibit abnormal collagen formation in the hypoxic penile conditions after RP [80]. The increased arterial inflow in the penis increases tissue oxygen levels, which effectively alleviates the tissue hypoxia damage caused by cavernous nerve injury. Due to these physiologic changes and effects, VEDs have become the centerpiece of penile rehabilitation protocols.

It is suggested that penile rehabilitation with VED should begin early after RP. Kohler et al. [81] found that early use of VED (1 month after RP) improved sexual function recovery and helped the preservation of penile length. Raina et al. [80] conducted a prospective study with 109 patients undergoing RP who were randomized to either undergo daily VED use for 9 months

starting 1 month after surgery or to receive no treatment. They found 17 % vs. 11 % recovery of erectile function with daily use of VED compared to non-VED use, and only 23 % VED user vs. 85 % non-VED users reported penile shrinkage. Dalkin et al. [82] did a study on 39 men who underwent nerve-sparing RP who had penile measurements before surgery and 3 months after surgery by a single investigator. Daily use of VED was begun on the day after catheter removal and continued for 90 days. Penile shortening ≥1.0 cm was considered significant. In men who complied well with VED therapy, only 1/36 (3 %) had a decrease of penile length ≥1.0 cm. Of the three men with poor VED compliance, two (67 %) had a reduction in penile length ≥1.0 cm. They concluded that their findings "strongly support a role for early intervention with the daily use of a VED in men wishing to preserve penile length." [82] There are clearly clinical suggestions that VED therapy improves erectile function and preserves penile size after RP likely due to its anti-hypoxic, anti-apoptotic, and anti-fibrotic mechanisms.

Penile Lengthening Strategies

In the USA, an estimated 10,000 men have undergone penile surgery for cosmetic reasons in the last decade [83]. Interestingly, a study by Mondaini et al. [84], showed that 85 % of the male patients in their cohort, which were men seeking penile lengthening, overestimated normal penile size by estimating "normal" penile length should range from 10 to 17 cm (median value of 12 cm). 15 % of men in their cohort were unable to estimate "normal" penile size. No patient in their cohort was found to have a penile length under the 2.5 percentile according to their nomogram [85]. They concluded that penile length is in fact normal in most men seeking penile lengthening procedures. Wessels et al. [9] proposed that only men with a flaccid length of less than 4 cm, or an erect length of less than 7.5 cm, should be considered candidates for lengthening procedures.

Furthermore, The Sexual Medicine Society of North America has drafted a position statement on penile lengthening and girth enhancement surgery. It reads as follows: "The Society for the Study of Impotence has found no peer-reviewed, objective or independently-monitored studies, or other data, which prove the safety or efficacy of penile lengthening and girth enhancement surgery. Therefore, penile lengthening and girth enhancement surgery can only be regarded as experimental surgery." Nonetheless, different surgical techniques have been studied for penile enhancement [86].

Lack of standardization of these controversial procedures has led to a wide variety of poorly documented surgical techniques, with varying results. Different techniques have been used for increasing penile girth with using either subcutaneous placement of different tissues (e.g., free fat, dermis graft, vascularized subcutaneous flaps) [9, 83] or cavernosal augmentation with saphenous grafts [87]. Perovic et al. [88] described the penile disassembly technique combined with the interposition of rib cartilage in the space between the glans cap and tips of the corpora cavernosa. They performed this procedure in 19 patients and found that the increase in penile length was 2–3 cm in 13 patients and 3–4 cm in the remaining six, with a mean follow-up of 3.3 years. There was no evidence of erosion, inflammation, or infection of the site of cartilage implantation as well as no injuries to the neurovascular bundle or urethra and no erectile dysfunction [88]. Their favorable reported results were not replicated and the technique did not become widespread.

One of the most common procedures for elongation of the penis is the release of the suspensory ligament in combination with advancement of an infrapubic skin flap onto the penis via an inverted V-Y skin plasty [89–91]. The drawbacks of this procedure include an abnormal appearance of bulky tissue at the base of the penis and a change in the angle of erection due to the possible development of a "low-hanging" penis [83]. In addition, one of the downsides of this technique is the penis reverting back to its original length, or even

sometimes shortening of the penis, due to reattachment of the suspensory ligament to the pubis [83]. Furthermore, although division of the suspensory ligament may increase penile length, it usually is not sufficient enough to satisfy the patient [92]. Thus, to improve the results of suspensory ligament release for penile lengthening, Shaeer et al. [93] described a technique in which suspensory ligament release was combined with "V-Y half-skin half-fat advancement flap" and a "T-closure." The authors reported an increase in the flaccid, outstretched penile length of 5.5 cm and noted no loss in the penile length gained six months after surgery. They were able to prevent any loss of penile length gained by advancing fat into the dead space, created by the descent of the corpora off the pubic bone, thereby creating a well-vascularized cushion upon which the corpora cavernosa sit, preventing reattachment. Furthermore, no complications were reported from this procedure.

With a similar goal of avoid the eventual loss of penile length that is initially gained following a release of the suspensory ligament with the inverted V-Y skin plasty, Srinivas et al. [94] reported a modification of the procedure. A silicone sheath was interposed between the pubic symphysis and suspensory ligament and, presumably due to this modification, length gain was effectively maintained at a follow-up of 6 months. Regardless of the specific surgical lengthening technique used, some authors recommend postoperative penile stretching using weights hung from the penis for several months after surgery [89]. The traction device could also theoretically be used postoperatively for this purpose, although no data exist to support this particular application.

Rolle et al. [95] have described the "sliding technique," in which IPP surgery is combined with double dorsal-ventral patch graft in an effort to lengthen the penis. In the sliding technique, a ventro-dorsal incision of the tunica albuginea is made in order to relax and lengthen the penis, IPP cylinders (that are longer than would otherwise be possible) are inserted and, finally, double dorsal–ventral patch grafting with porcine small intestinal submucosa is utilized to cover the tunical defects. They reported the results in three patients with PD and penile shortening and benefited from an average increase in length of about 3.2 cm at follow-up of 13 months. There was no significant loss of sensitivity or signs of impaired vascularity in this case series.

Recently, Edygio et al. [96] described a modified "sliding technique" for penile length as well as girth restoration with concomitant IPP implantation. Their technique is based on three elements: (1) the sliding maneuver for penile length increase (similar to that described above) (2) potential complementary longitudinal ventral and/or dorsal tunical incisions for girth restoration, and (3) closure of the newly created rectangular bow-shaped tunical defects with Buck's fascia only. They reported their results on 143 patients who underwent this procedure and demonstrated a mean penile length gain of 3.1 cm (range, 2–7 cm) at a median follow up of 9.7 months. They also noted no major intraoperative or postoperative complications. Although postoperative hematomas at the base of the penile shaft occurred in 35 total patients (24.2 %), all resolved spontaneously with observation. Seven patients (4.9 %) also experienced temporary partial glans numbness, which again resolved in the follow-up period [96]. In a multicenter prospective study, Sansolone et al. [97] have also recently evaluated penile lengthening with circumferential graft/tunical incision during IPP surgery in patients with PD and severe penile shortening. With an average follow-up of 22 months, an average penile length gain was 2.8 cm and 90 % of patients reported being satisfied with the cosmetic and functional result of the surgery.

Conclusions

Penile length/size is a major concern for men across various cultures. It has been linked to self-esteem and sexual identity. It is important for urologists to recognize the impact of urological conditions, therapies, and surgeries on penile size and shape. Patients should be counseled accordingly, particularly because loss of penile length is

associated with devastating psychological consequences. Better understanding and recognition of penile length loss issues that can help practitioners are needed in order to minimize shortening of penile size. Multiple treatment options for penile shortening and curvature in PD are available, but some PD treatments (i.e., plication) actually shorten penile length. Penile lengthening procedures are controversial and rarely performed, but technical innovations to the sliding technique are promising.

References

1. Vardi Y, Harshai Y, Gil T, Gruenwald I. A critical analysis of penile enhancement procedures for patients with normal penile size: surgical techniques, success, and complications. Eur Urol. 2008;54: 1042–50.
2. Talalaj JTS. The strangest human sex, ceremonies and customs. Melbourne: Hill of Content; 1994.
3. Lever J, Frederick DA, Peplau LA. Does size matter? Men's and women's views on penis size across the lifespan. Psychol Men Masculinity. 2006;7(3): 129–43.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
5. Mattelaer J, Jilek W. Koro—the psychological disappearance of the penis. J Sex Med. 2007;4(5): 1509–15.
6. Barnes HV. Physical growth and development during puberty. Med Clin North Am. 1975;59: 1305–17.
7. Veale D, Miles S, Bramley S, Muir G, Hodsoll J. Am I normal? A systematic review and construction of nomograms for flaccid and erect penis length and circumference in up to 15,521 men. BJU Int. 2015; 115(6):978–86.
8. Promodu K, Shanmughadas KV, Bhat S, Nair KR. Penile length and circumference: an Indian study. Int J Impot Res. 2007;19:558–63.
9. Wessells H, Lue TF, McAninch JW. Penile length in the flaccid and erect states: guidelines for penile augmentation. J Urol. 1996;156(3):995–7.
10. Ohebshalom M, Mulhall J, Guhring P, Parker M. Measurement of penile curvature in Peyronie's disease patients: comparison of three methods. J Sex Med. 2007;4(1):199–203.
11. Matsushita K, Stember DS, Nelson CJ, Mulhall JP. Concordance between patient and physician assessment of the magnitude of Peyronie's disease curvature. J Sex Med. 2014;11(1):205–10.
12. Johannes CB, Araujo AB, Feldman HA, et al. Incidence of erectile dysfunction in men 40 to 69 years old: Longitudinal results from the Massachusetts Male Aging Study. J Urol. 2000; 163:460–3.
13. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA. 1993;270:83.
14. Osterberg EC, Maganty A, Ramasamy R, Eid JF. Pharmacologically induced erect penile length and stretched penile length are both good predictors of post-inflatable prosthesis penile length. Int J Impot Res. 2014;26(4):128–31.
15. Deveci S, Martin D, Parker M, Mulhall JP. Penile length alterations following penile prosthesis surgery. Eur Urol. 2006;51:1128–31.
16. Levine LA. Peyronie's disease and erectile dysfunction: Current understanding and future direction. Ind J Urol. 2010;22(3):246–50.
17. Chitale S, Morsey M, Sethia K. Is penile shortening part of natural history of Peyronie's disease? Open Urol Nephr J. 2010;3:16–20.
18. Langston JP, Carson CC. Peyronie disease: plication or grafting. Urol Clin North Am. 2011;38(2): 207–16.
19. Nelson C, Diblasio C, Kendirci M, Hellstrom W, Guhring P, Mulhall JP. The chronicity of depression and distress in men with Peyronie's disease. J Sex Med. 2008;5:185–90.
20. Kadioglu A, Akman T, Sanli O, Gurkan L, Cakan M, Celtik M. Surgical treatment of Peyronie's disease: a critical analysis. Eur Urol. 2006;50(2):235–48.
21. Kumar R, Nehra A. Surgical and minimally invasive treatments for Peyronie's disease. Curr Opin Urol. 2009;19(6):589–94.
22. Gelbard MK, Dorey F, James K. The natural history of Peyronie's disease. J Urol. 1990;144(6):1376–9.
23. Prieto Castro RM, Leva Vallejo ME, Regueiro L, Curado A, Kindelan JA, Requena Tapia MJ. Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. BJUI Int. 2003;91(6):522–4.
24. Pryor JP, Farrell CR. Controlled clinical trial of vitamin E in Peyronie's disease. Prog Reprod Biol Med. 1983;9:41–5.
25. Safarinejad MR, Hosseini SY, Kolahi AA. Comparison of vitamin E and propionyl-L-carnitine, separately or in combination, in patients with early chronic Peyronie's disease: a double-blind, placebo controlled, randomized study. J Urol. 2007;178 (4 Pt 1):1398–403.
26. Mulhall JP, Anderson MS, Lubrano T, Shankey TV. Peyronie's disease cell culture models: phenotypic, genotypic, and functional analyses. Int J Impot Res. 2002;14(5):397–405.
27. Roth M, Eickelberg O, Kohler E, Erne P, Block LH. Ca2þ channel blockers modulate metabolism of collagens within the extra-cellular matrix. Proc Natl Acad Sci U S A. 1996;93:5478–82.

28. Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. J Urol. 1997;158(4):1395–9.
29. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. J Urol. 2002;168(2):621–5.
30. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. J Urol. 1994;151(6):1522–4.
31. Shirazi M, Haghpanah AR, Badiee M, et al. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. Int Urol Nephrol. 2009; 41(3):467–71.
32. Gelbard M, Lipshultz L, Tursi J, Smith T, Kaufman G, Levine LA. Phase 2b study of the clinical efficacy and safety of collagenase clostridium histolyticum in patients with Peyronie's disease. J Urol. 2012; 187(6):2268–74.
33. Gelbard M, Goldstein I, Hellstrom W, McMahon C, Smith T, Tursi J, Jones N, Kaufman G, Carson C. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie disease in 2 large double-blind randomized, placebo-controlled phase 3 studies. J Urol. 2013;190:199–207.
34. Levine LA, Newell MM. FastSize medical extender for the treatment of Peyronie's disease. Expert Rev Med Devices. 2008;5(3):305–10.
35. Gontero P, Di Marco M, Giubilei G, Bartoletti R, Pappagallo G, Tizzani A. Use of penile extender device in the treatment of penile curvature as a result of Peyronie's disease. Results of phase II prospective study. J Sex Med. 2008;6(2):558–66.
36. Ralph DJ, Gonzalez-Cadvid N, Mirone V, Perovic S, Sohn M, Usta M, Levine L. The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med. 2010;7(7):2359–74.
37. Kadioglu A, Kucukdurmaz F, Sanli O. Current status of the surgical management of Peyronie's disease. Nat Rev Urol. 2011;8(2):95–106.
38. Smith JF, Walsh TJ, Lue TF. Peyronie's disease: a critical appraisal of current diagnosis and treatment. Int J Impot Res. 2008;20(5):445–59.
39. Ding S, Lu J, Zhang H, Wei L, Ding K. A novel modification of tunical plication by plaque thinning: long-term results in treating penile curvature of Peyronie's disease. Int Urol Nephrol. 2010;42(3): 597–602.
40. Horstmann M, Kwol M, Amend B, Hennenlotter J, Stenzi A. A self-reported long-term follow-up of patients operated with either shortening techniques or a TachoSil grafting procedure. Asian J Androl. 2011;13(2):326–31.
41. Paez A, Mejias J, Vallejo J, Romero I, de Castro M, Gimeno F. Long-term patient satisfaction after surgical correction of penile curvature via tunical plication. Int Braz J Urol. 2007;33(4):502–7.
42. Van Der Horst C, Martinez Portillo FJ, Seif C, Alken P, Juenemann KP. Treatment of penile curvature with Essed-Schroder tunical plication: aspects of quality of life from the patients' perspective. BJU Int. 2004;93:105–8.
43. Kendirci M, Hellstrom WJ. Critical analysis of surgery for Peyronie's disease. Curr Opin Urol. 2004;14(6):381–8.
44. Levine LA, Larsen SM. Surgery for Peyronie's disease. Asian J Androl. 2013;15(1):27–34.
45. Pendleton CM, Wang R. Peyronie's disease: current therapy. Transl Androl Urol. 2013;2(1):15–23.
46. Syed AH, Abbasi Z, Hargreave TB. Nesbit procedure for disabling Peyronie's curvature: a median follow-up of 84 months. Urology. 2003;61(5): 999–1003.
47. Gelbard MK, Hayden B. Expanding contractures of the tunica albuginea due to Peyronie's disease with temporalis fascia free grafts. J Urol. 1991; 145(4):772–6.
48. Gur S, Limin M, Hellstrom WJ. Current status and new developments in Peyronie's disease: medical, minimally invasive and surgical treatment options. Expert Opin Pharmacother. 2011;12(6):931–44.
49. Kadioglu A, Sanli O, Akman T, Ersay A, Guven S, Mammadov F. Graft materials in Peyronie's disease surgery: a comprehensive review. J Sex Med. 2007;4(3):581–95.
50. Breyer BN, Brant WO, Garcia MM, Bella AJ, Lue TF. Complications of porcine small intestine submucosa graft for Peyronie's disease. J Urol. 2007;177(2):589–91.
51. Knoll LD. Use of small intestinal submucosa graft for the surgical management of Peyronie's disease. J Urol. 2007;178(6):2474–8.
52. Brannigan RE, Kim ED, Oyasu R, McVary KT. Comparison of tunica albuginea substitutes for the treatment of Peyronie's disease. J Urol. 1998;159(3):1064–8.
53. Levine LA, Greenfield JM, Estrada CR. Erectile dysfunction following surgical correction of Peyronie's disease and a pilot study of the use of sildenafil citrate rehabilitation for postoperative erectile dysfunction. J Sex Med. 2005;2(2):241–7.
54. Taylor FL, Abern MR, Levine LA. Prediciting erectile dysfunction following surgical correction of Peyronie's disease without inflatable penile prosthesis placement: vascular assessment and preoperative risk factors. J Sex Med. 2012;9(1):296–301.
55. Levine LA, Dimitriou RJ. A surgical algorithm for penile prosthesis placement in men with erectile failure and Peyronie's disease. Int J Impot Res. 2000;12(3):147–51.
56. Levine LA, Estrada CR. Human cadaveric pericardial graft for the surgical correction of Peyronie's disease. J Urol. 2003;170(6 Pt 1):2359–62.
57. Wilson SK, Delk 2nd JR. A new treatment for Peyronie's disease: modeling the penis over an

inflatable penile prosthesis. J Urol. 1994; 152(4):1121–3.
58. Rahman NU, Carrion RE, Bochinski D, Lue TF. Combined penile plication surgery and insertion of penile prosthesis for severe penile curvature and erectile dysfunction. J Urol. 2004;171(6 Pt 1): 2346–9.
59. Mulhall JP, Slovick R, Hotaling J, Aviv N, Valenzuela R, Waters WB, Flanigan RC. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. J Urol. 2002;167(3):1371–5.
60. Parekh A, Chen MH, Hoffman KE, Choueiri TK, Hu JC, Bennett CL, Kattan MW, Sartor O, Stein K, Graham PL, D'Amico AV, Nguyen PL. Reduced penile size and treatment regret in men with recurrent prostate cancer after surgery, radiotherapy plus androgen deprivation, or radiotherapy alone. Urology. 2013;81(1):130–4.
61. Fraiman MC, Lepor H, McCullough AR. Changes in penile morphometrics in men with erectile dysfunction after nerve-sparing radical retropubic prostatectomy. Mol Urol. 1999;3(2):109–15.
62. Munding MD, Wessells HB, Dalkin BL. Pilot study of changes in stretched penile length 3 months after radical retropubic prostatectomy. Urology. 2001;58(4):567–9.
63. Savoie M, Kim SS, Soloway MS. A prospective study measuring penile length in men treated with radical prostatectomy for prostate cancer. J Urol. 2003;169(4):1462–4.
64. Engel JD, Sutherland DE, Williams SB, Wagner KR. Changes in penile length after robot-assisted laparoscopic radical prostatectomy. J Endourol. 2011;25(1):65–9.
65. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from health professional follow-up study. Ann Intern Med. 2003;139:161–8.
66. Costello AJ, Brooks M, Cole OJ. Anatomical studies of the neurovascular bundle and cavernosal nerves. BJU Int. 2004;94(7):1071–6.
67. Oster JR, Epstein M. Use of centrally acting sympatholytic agents in the management of hypertension. Arch Intern Med. 1991;151:1638–44.
68. McCullough AR. Penile change following radical prostatectomy: size, smooth muscle atrophy, and curve. Curr Urol Rep. 2008;9(6):492–9.
69. Gontero P, Galzerano M, Bartoletti R. New insights into the pathogenesis of penile shortening after radical prostatectomy and the role of postoperative sexual function. J Urol. 2007;178(2):602–7.
70. Carlsson S, Nilsson AE, Johansson E, Nyberg T, Akre O, Steineck G. Self-perceived penile shortening after radical prostatectomy. Int J Impot Res. 2012;24(5):179–84.
71. Briganti A, Fabbri F, Salonia A, Gallina A, Chun FK, Deho F. Preserved postoperative penile size correlates well with maintained erectile function after bilateral nerve-sparing radical retropubic prostatectomy. Eur Urol. 2007;52:702–7.
72. Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. Int J Impot Res. 1998;10(2): 113–20.
73. Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. J Urol. 2005; 173(5):1673–6.
74. Mulhall JP. Penile length changes after radical prostatectomy. BJU Int. 2005;96(4):472–4.
75. Klein LT, Miller MI, Buttyan R, Raffo AJ, Burchard M, Devris G, Cao YC, Olsson C, Shabsigh R. Apoptosis in the rat penis after penile denervation. J Urol. 1997;158(2):626–30.
76. User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT. Penile weight and cell subtyped specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol. 2003;169(3): 1175–9.
77. Zhou S, Chen LS, Miyauchi Y, Miyauchi M, Kar S, Kangavari S, Fishbein MC, Sharifi B, Chen PS. Mechanisms of cardiac nerve sprouting after myocardial infarction in dogs. Circ Res. 2004;95:76–83.
78. Hall SJ, Basile G, Bertero EB, de las Morenas A, Goldstein I. Extensive corporeal fibrosis after penile irradiation. J Urol. 1995;153(2):372–7.
79. Yuan J, Westney OL, Wang R. Design and application of a new rat-specific vacuum erectile device for penile rehabilitation research. J Sex Med. 2009;6:3247–53.
80. Raina R, Agarwal A, Ausmundson S, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. Int J Impot Res. 2006;18:77–81.
81. Kohler TS, Pedro R, Hendlin K, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU Int. 2007;100:858–62.
82. Dalkin BL, Christopher BA. Preservation of penile length after radical prostatectomy: early intervention with a vacuum erection device. Int J Impot Res. 2007;19:501–4.
83. Alter GJ. Aesthetic genital surgery. Aesthetic surgery of the male genitalia. In: Richard ME, Gary JA, editors. Reconstructive and plastic surgery of the external genitalia. Adult and pediatric. Philadelphia: W.B. Saunders Company; 1999. p. 46–70.
84. Mondaini N, Ponchietti R, Gontero P, Muir GH, Natali A, Caldarera E, Biscioni S, Rizzo M. Penile length is normal in most men seeking penile lengthening procedures. Int J Impot Res. 2002;14(4): 283–6.
85. Ponchietti R, Mondaini N, Bonafe M, Di Loro F, Biscioni S, Masieri L. Penile length and circumference:

a study on 3,300 young Italian males. Eur Urol. 2001;39(2):183–6.
86. Dillon BE. Chama, Honig SC. Penile size and penile enlargement surgery: a review. Int J Impot Res. 2008;20(5):519–29.
87. Austoni E, Guarneri A, Cazzaniga A. A new technique for augmentation phalloplasty: albugineal surgery with bilateral saphenous grafts—three years of experience. Eur Urol. 2002;42(3):245–53.
88. Perovic SV, Djordjevic MLJ. Penile lengthening. BJU Int. 2000;86(9):1028–33.
89. Alter GJ. Penile enhancement. In: McGuire EJ, editor. Advances in urology, vol. 9. St Louis: Mosby; 1996. p. 225–54.
90. Johnston JH. Lengthening of the congenital or acquired small penis. BJU Int. 1974;46(6):685–7.
91. Shirong L, Xuan Z, Zhengxiang W, Dongli F, Julong W, Dongyun Y. Modified penis lengthening surgery: review of 52 cases. Plast Reconstr Surg. 2000;105(2):596–9.
92. Li CY, Kayes O, Kell PD, Christopher N, Minhas S, Ralph DJ. Penile suspensory ligament division for penile augmentation: indications and results. Eur Urol. 2006;49(4):729–33.
93. Shaeer O, Shaeer K, el-Sebaie A. Minimizing the losses in penile lengthening: "V-Y half-skin half-fat advancement flap" and "T-closure" combined with severing the suspensory ligament. J Sex Med. 2006;3(1):155–60.
94. Srinivas BV, Vasan SS, Sajid M. Penile lengthening procedure with V-Y advancement flap and an interposing silicone sheath: A novel methodology. Indian J Urol. 2012;28(3):340–2.
95. Rolle L, Ceruti C, Timpano M, Sedigh O, Destefanis P, Galleto E, Falcone M, Fontana D. A new, innovative, lengthening surgical procedure for Peyronie's disease by penile prosthesis implantation with double dorsal-ventral patch graft: the "sliding technique". J Sex Med. 2012;9(9):2389–95.
96. Egydio PH, Kuehhas FE. Penile lengthening and widening without grafting according to a modified 'sliding'technique. BJU Int. 2015;116(6):965–72.
97. Sansalone S, Garaffa G, Djinovic R, Egydio P, Vespasiani G, Miano R, Loreto C, Ralph DJ. Simultaneous penile lengthening and penile prosthesis implantation in patients with Peyronie's disease, refractory erectile dysfunction, and severe penile shortening. J Sex Med. 2012;9(1):316–21.
98. Taylor FL, Levine LA. Surgical correction of Peyronie's disease via tunica albuginea plication or partial plaque excision with pericardial graft: long-term follow up. J Sex Med. 2008;5(9):2221–8.
99. Daitch JA, Angermeier KW, Montague DK. Modified corporoplasty for penile curvature: long-term results and patient satisfaction. J Urol. 1999;162(6): 2006–9.
100. Rehman J, Benet A, Minsky LS, Melman A. Results of surgical treatment for abnormal penile curvature: Peyronie's disease and congenital deviation by modified Nesbit plication (tunical shaving and plication). J Urol. 1997;157(4):1288–91.
101. Gholami SS, Lue TF. Correction of penile curvature using the 16-dot plication technique: a review of 132 patients. J Urol. 2002;167(5):2066–9.
102. Dugi DD, Morey AF. Penoscrotal plication as a uniform approach to reconstruction of penile curvature. BJU Int. 2010;105(10):1440–4.
103. Chung E, Clendinning E, Lessard L, Brock G. Five-year follow-up of Peyronie's graft surgery: outcomes and patient satisfaction. J Sex Med. 2011; 8(2):594–600.
104. Simonato A, Gregori A, Varca V, Venzano F, De Rose AF, Ambruosi C, Esposito M, Carmignani G. Penile dermal flap in patients with Peyronie's disease: long-term results. J Urol. 2010;183(3): 1065–8.
105. Cormio L, Zucchi A, Lorusso F, Selvaggio O, Fioretti F, Porena M, Carrieri G. Surgical treatment of Peyronie's disease by plaque incision and grafting with buccal mucosa. Eur Urol. 2009;55(6): 1469–75.
106. El-Sakka AL, Rashwan HM, Lue TF. Venous patch graft for Peyronie's disease. Part II: outcome analysis. J Urol. 1998;160(6 Pt 1):2050–3.
107. Craatz S, Spanel-Borowski K, Begemann JF, Olianas R, Fisch M, Hohenfellner R. The dorsal lamina of the rectus sheath: a suitable grafting material for the penile tunica albuginea in Peyronie's disease? BJU Int. 2006;97(1):134–7.
108. O'Donnell PD. Results of surgical management of Peyronie's disease. J Urol. 1992;148(4):1184–7.
109. Goyal NK, Kumar A, Das SK, Pandey AK, Sharma GK, Trivedi S, Dwivedi US, Singh PB. Experience with plaque excision and dermal grafting in the surgical treatment of Peyronie's disease. Singapore Med J. 2008;49(10):805–8.
110. Levine LA, Benson J, Hoover C. Inflatable penile prosthesis placement in men with Peyronie's disease and drug-resistant erectile dysfunction: A single-center study. J Sex Med. 2010;7(11):3775–83.
111. Austoni E, Colombo F, Romano AL, Guarneri A, Kartalas GI, Cazzaniga A. Soft prosthesis implant and relaxing albugineal incision with saphenous grafting for surgical therapy of Peyronie's disease: a 5-year experience and long-term follow-up on 145 operated patients. Eur Urol. 2005;47:223–9.
112. Grasso M, Lania C, Fortuna F, Blanco S, Piacentini I. Preservation of cavernosal erectile function after soft penile prosthesis implant in Peyronie's disease: long-term follow-up. Adv Urol 2008;646052.
113. Shaeer O. Trans-corporal incision of Peyronie's plaques. J Sex Med. 2011;8:589–93.

Penile Rehabilitation After Prostate Cancer Treatments

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Introduction

Despite recent controversy surrounding PSA screening in men, screening for and treatment of prostate cancer (PC) continues. Much of the argument against the treatment of PC has been based on risks of treatment as erectile dysfunction (ED) and incontinence are major quality of life factors. While this chapter does not focus on prevention of incontinence, there is continued interest in preservation of erectile function (EF) after PC treatments to mitigate these risks.

The preservation of EF after PC treatments largely takes the effect of prevention at the time of surgery through nerves sparing techniques and recuperation postoperatively with penile rehabilitation. Putatively, in these postoperative men, the oxygenating effects of natural spontaneous and provoked erections is replaced with either pharmacologically or mechanically induced erections to nourish the cavernosal smooth muscle tissue during a, hopefully temporary, loss of EF. When the integrity of the cavernosal smooth muscle is not protected, penile fibrosis may occur leading to penile shortening and possible permanent ED.

Prevalence of ED After PC Treatment

There exist large variations in the reported rates of ED following PC treatment. This wide range of reported ED can likely be attributed to the difficulties in performing a prevalence study. Some of these difficulties include variance in definitions of ED used, methodology and timing of evaluations and lack of information on pretreatment potency.

More recent studies have attempted to delineate between these confounding factors in order to more accurately assess pretreatment risk factors for PC treatment side effects. Resnick et al., through their Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study, captured data on the pretreatment status of the common side effects of PC treatment from the newly diagnosed. The authors reported a 43 %

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ED prevalence of patients diagnosed with PC in the previous 6 months, before any treatment was even initiated [1].

The two most accepted treatment options for PC control—radiation or surgery—also affect ED rates and occurrence differently. However, this may be somewhat contaminated by the fact that patients undergoing surgery are more likely to use erectogenic aids after PC treatment [2]. As there are certainly differences in these different treatments for PC, they are discussed separately below when possible.

Radical Prostatectomy

Invariably, some degree of sexual dysfunction occurs immediately after radical prostatectomy (RP). Patients will usually experience at least temporary loss of erections, including nocturnal erections [3]. The etiology of ED resulting from RP seems to be multifactorial but is predominantly due to the intraoperative damage to the nerves surrounding the prostate. Many patients will experience some recovery in EF over a 12–16 month period, as the neuropraxia slowly resolves. As such, 12 and 24 month potency rates after surgery range from 54 to 90 % and 63 to 94 %, respectively [4]. However, several longer-term follow-up studies have shown some form of continued ED many years after the initial surgery [5]. While the cavernous nerves were previously thought to be discrete entities in a neurovascular bundle, recent work has shown that the nerves controlling erectile function are likely more complicated and diffuse [6, 7].

With the change from open retropubic RP to robotic assisted laparoscopic prostatectomy (RALP) there has potentially been an improvement in patient centered outcomes. One of the key aspects of erection preservation in surgery is performance of neurovascular bundle-sparing, which may be more commonly done in robotic surgery [8], possibly due to better visualization. A recently published prospective, controlled, nonrandomized trial from Europe did find outcomes in all areas of EF assessed favoring RALP over RRP 12 months after surgery. After adjusting for potentially confounding factors such as age, smoking status, or cardiovascular disease, patients treated with RALP had a 5 % lower absolute rate of ED than those undergoing retropubic RP [8]. A large meta-analysis also reported cumulative data favoring RALP to retropubic RP with a 47.8 % vs. a 24.2 % potency rate, respectively [4].

Radiation

Since radiation therapy (RT) became a treatment option for men with PC in the 1970s, resulting ED has been a known side effect. Reported incidence, however, falls victim to the same discrepancies as RP, as studies vary widely in methodology. Additional difficulty in capturing the true incidence of ED after RT is the necessity of a longer follow-up study, as EF is known to deteriorate more distantly with RT than surgery. Rates from prospective studies show a range of ED rates, from 36 to 59 % after external beam radiotherapy and 24–50 % after brachytherapy [9].

Etiology of Post-radiation ED

The fundamental efficacy of RT in cancer treatment is induction of DNA damage to destroy cancerous cells. The inevitable consequence of damage to surrounding, healthy tissues is the cause of many unfortunate side effects. Radiation doses to areas critical for EF include the neurovascular bundles, internal pudendal arteries, accessory pudendal arteries, corpora cavernosa, and the penile bulb [10]. While the radiation field includes damage to at least all the aforementioned structures, studies to determine the exact etiology of RT induced ED have historically pointed toward a more pronounced arteriogenic dysfunction [11, 12]. Additionally alleged mechanisms include corporal fibrosis [13], and nerve injury [14].

More recent studies continue to validate vascular damage as the predominant means of ED from RT. In an animal model study, all irradiated rats demonstrated vascular changes in their penile arteries, including apoptosis in the smooth

muscle layer, thickening of arterial walls, and thrombosis [10]. A human study using dynamic infusion cavernosometry/cavernosography demonstrated combined arterial and venous insufficiency of patients with ED at a mean 11 months following RT [15].

Radiation Dose

In most cases, the radiation dose delivered to tissues determines the severity of resulting unintended effects. This is especially true regarding systemic symptoms from radiation sickness, where effects from a high dose of radiation can be felt almost immediately [16]. However, the few studies evaluation radiation dose from PC treatment have not demonstrated a clear relationship between radiation dose and resulting ED. Attempts to reduce radiation exposure during external beam radiation therapy (EBRT) to the penile bulb [9] or corpora cavernosa [17] yielded no correlation between ED at 2 years. Cancer control remains the most important factor in determining radiation dose, and further studies must be performed before reductions in dosage can be considered for erectile preservation.

Brachytherapy

ED rates after brachytherapy appear to be somewhat lower compared to EBRT. One study found a 6 year potency preservation rate of 52 % with 92 % achieving potency if also receiving pharmacological support with sildenafil [18]. However, the use sildenafil in this cohort inherently implies ED and this comparison is dubious. The multivariate analysis was interesting as it revealed no significant correlation to erection preservation with radiation dose, choice of isotope, or clinical stage, but did find significance to pretreatment EF, supplemental EBRT, and history of diabetes mellitus. Another study yielded similar results, with an EF preservation rate of 59 % at 5 years after brachytherapy alone for treatment of PC although new PDE5I use was not considered a failure for EF preservation [19].

Comparison of ED Between Surgery and Radiation

Comparison studies have shown that while both RP and RT lead to diminished erections, the initial dysfunction is more severe with surgery but more likely to improve over time [20]. In contrast, EF is more preserved initially in patients who received RT, but their recovery is diminished and between year two to five, experiences a considerable decline [21]. Therefore, the rates of ED stemming from PC therapy are not convincingly different between treatment choices.

However, the length of time until equivalent outcomes may be important to patients, as it may be at least 5 years before rates of decline stabilize. This was shown in a long-term study in which patients receiving either RT or surgery were followed at 2, 5, and 15 years. Men who had undergone RP were significantly more likely to report ED than the RT group at both 2 and 5 years. However, at 15 years the rates were nearly identical. When rates were controlled for baseline sexual functioning, no treatment based difference was found starting at 5 years [22].

Defining Success in Penile Rehabilitation

EF may be defined by objective measures or patient reported ability to engage in intercourse. In fact, a meta-analysis looking at studies from 1985 to 2007 found 22 different unique definitions of favorable EF in studies. Many definitions were more objective, using specific numerical values on validated questionnaires, while other definitions were more indistinct (“reported intercourse,” “potent”) [23].

While the validated questionnaires for ED, invariably measure different parts of sexual function as a continuous variable, there is likely a minimum value at which patients are satisfied and able to perform to their expectations. The work by Briganti et al. looked at men undergoing bilateral nerve sparing retropubic RP to define a goal at

which patient satisfaction matched up with International Index of Erectile Function (IIEF) domains [24]. Overall sexual satisfaction was decreased if patients who had normal potency preoperatively (IIEF-EF>26) but had a score less than 22 after surgery. From their findings, the authors hypothesized that if potent patients are able to maintain a score of at least 22 on the IIEF-EF, they will likely be satisfied with their EF after RP.

Rehabilitation Practice Patterns

Despite improvements in post-RP EF with rehabilitation, there is still not a standardized protocol for rehabilitation and enthusiasm for rehabilitation protocols continues to be irregular. In a study by the French Urologic Association, 64 % of physicians did not routinely recommend rehabilitation. Scheduled intracavernosal injection (ICI) was the most common rehabilitation protocol with on demand ICI and scheduled phosphodiesterase type 5 inhibitor (PDE5I) being the next most common. The most frequent duration of treatment was 1 year with younger physicians and physicians performing more RP were likely to recommend a rehabilitation protocol overall [25].

American Urologic Association (AUA) members were analyzed in a study including 618 urologists who participated in an e-mail survey. The majority of respondents recommended penile rehabilitation (86 %) but only 43 % recommended a protocol for all patients after RP. Factors that influenced recommendation for rehabilitation included preoperative EF (66 %), nerve sparing technique (22 %), and patient age (5 %). PDE5I followed by vacuum erection device (VED) were the most commonly utilized protocols. Encouragingly, practitioners who performed RP or identified as uro-oncologists were more likely to recommend penile rehabilitation [26].

An assessment of International Society of Sexual Medicine (ISSM) members found that a similar number of respondents (87 %) recommended some form of rehabilitation [27]. Utilization was correlated with uro-oncology training, performing RP and seeing more than 50 patients per year who had RP. About half of polled members started rehabilitation at catheter removal with PDE5I still the most commonly used approach (95 %), with ICI (75 %) and VED (30 %) also being popular choices. In those that did not routinely recommend rehabilitation, half stated that they found the cost prohibitive with 25 % each stating they were not familiar with the concept or were not convinced by the evidence.

Predicting Factors for Return of EF After Treatment

EF recovery rates are variable based on multiple factors and are largely influenced by reporting bias. In their meta-analysis, Tal et al. found that overall EF recovery rates were higher in single surgeon series and studies following patients for greater than 18 months [23]. This is not surprising as these studies can often serve as surgeon advertisements.

In some studies, patient factors have been identified that may be correlated with better postoperative outcomes. Patient age [23, 28–32], some degree of nerve sparing [28, 31–35], and, not surprisingly, better preoperative EF [29–33, 35] have been shown to be predictive of better EF after surgery. Comorbidities have also been identified as a detrimental factor [30, 32, 33].

Timing of Rehabilitation

When determining the optimal modality of a penile rehabilitation program, consideration must also be given to the timing of program initiation. Histopathologic data derived from both animal and human studies suggest that earlier rehabilitation may be more efficacious in the preservation of corpora smooth muscle, and resultantly, EF.

User et al. evaluated rates of apoptosis among rat corpus cavernosa smooth muscle following unilateral or bilateral cavernous neurotomy [36]. Significant apoptosis of smooth muscle was seen in both groups as early as postoperative day 1. By postoperative day 60, rates of apoptosis had

decreased to preoperative levels, possibly signifying a permanent change. In a compelling human study by Iacono et al. 19 patients with normal preoperative EF undergoing radical prostatectomy (RP) also underwent corpora cavernosa biopsy at the time of surgery, as well as two and 12 months postoperatively [37]. No penile rehabilitation program was employed. At the first postoperative biopsy, smooth muscle content was significantly decreased, while collagen content was significantly increased compared with preoperative biopsies. A temporal trend was also noted, as smooth muscle again decreased significantly with increase in collagen content at 12 months when compared to 2 months.

In an assessment of early (<6 months after RP) vs. late (>6 months) initiation of rehabilitation, postoperative EF was followed serially in 84 patients with organ-confined PC who had presented for management of ED following bilateral nerve-sparing RP [38]. All patients were started on a penile rehabilitation program consisting of 100 mg sildenafil citrate on-demand with a goal of three erections per week. If unsuccessful, patients were then started on injection therapy. At 2 year follow-up, there was a significant difference in the IIEF-EF domain between the early and late groups (22 vs. 16, $p<0.001$) with a higher percentage of men in the early group having medication-unassisted functional erections (59 % vs. 30 %, $p<0.01$). Similar clinical findings were seen in a small cohort of patients who underwent cystoprostatectomy wherein the authors found objective improvement using penile Doppler studies in the group starting rehabilitation at 2 months instead of 6 months [39].

While the urologic oncologist may be more likely to focus on the patient's tumor markers or continence in the postoperative period, they should not neglect the return of adequate EF. A delay in the return of corporal smooth muscle oxygenation may encourage apoptosis, fibrosis, and penile shortening. The crucial need to start rehabilitation early was demonstrated by the progressive decrease in EF noted with time from surgery in patients assessed by penile Doppler [40].

Specific Strategies

Intracavernosal Injections

The concept of penile rehabilitation was first introduced in a groundbreaking study by Montorsi et al. examining the effect of postoperative ICI with alprostadil on the recovery of spontaneous EF after RP [41]. Thirty patients were randomized to alprostadil ICI three times per week for 12 weeks, or observation. Primary outcomes were subjective EF, penile Doppler and nocturnal erection testing at 6 months. Of the 15 patients randomized to the treatment group, 12 (80 %) completed the treatment schedule. Of these, eight patients (67 %) reported recovery of EF sufficient for sexual intercourse, compared to three patients (20 %) in the comparison group ($p<0.01$). In the treatment group, ten patients (83 %) were found to have normal penile hemodynamics on Doppler ultrasound, compared to only three patients who did not rehabilitate. Finally, nocturnal testing showed normal erectile activity in seven patients in the alprostadil group and three patients in the comparison group. While a pioneering concept and study, they did not include a placebo treatment or preoperative assessment of EF.

Relatively few studies have followed this seminal work. The small prospective study of 87 patients by Yiou et al. reported increases in EF as determined by IIEF [42]. Improvements in IIEF were actually seen between 6 (14.0) and 12 months (17.2, $p<0.03$). Despite a general lack of high quality studies verifying the efficacy, ICI is a good overall treatment option for rehabilitation protocols especially in men who underwent non-nerve sparing RP and will correspondingly not respond to PDE5Is. While the AUA guidelines recommend the use of ICI in select patients who fail oral medical options [43], the clinician should consider quickly advancing to this option in men who did not undergo some degree of nerve sparing during RP. Previous work has demonstrated an improvement in corporal oximetry with ICI [44].

Intraurethral Alprostadil

Only one randomized, prospective trial looking at the use of intraurethral alprostadil (IUA) as part of a penile rehabilitation program has been reported. McCullough et al. randomized 212 men with normal preoperative EF following nerve-sparing RP to nightly 125 mcg IUA or 50 mg oral sildenafil citrate [45]. At 1 year postoperatively, there were no statistically significant differences between the groups in IIEF-EF domain scores or intercourse success rates, lending support to non-inferiority of IUA. However, there was a likely a bias in favor of IUA responders as the group had a higher dropout rate. A similarly high dropout rate was noted in a non-randomized, prospective study assessing varying doses of IUA or no ED aids. Only 68 % of patients receiving IUA completed the 6 month treatment course, although 74 % reported successful intercourse, compared to only 37 % of the untreated control group [46].

While the current literature surrounding IUA is largely incomplete, it can still be included in part of a rehabilitation protocol but will unlikely succeed as the primary agent for treatment, although this role has never been adequately assessed. When studied in combination with oral PDE5I or a penile constriction device, increased effectiveness has been noted in rehabilitation outcomes [47–49].

PDE5 Inhibitors

Animal Studies

A multitude of evidence in animal models supports the use of PDE5Is in penile rehabilitation programs. Numerous rodent studies have demonstrated meaningful histopathologic changes in penile tissue following administration of PDE5Is. In a study of rats following bilateral cavernous nerve resection, Ferrini et al. demonstrated preservation of smooth muscle content and inhibition of corporal fibrosis in rats who had received long-term vardenafil treatment [50]. Furthermore, vardenafil was found to prevent veno-occlusive dysfunction as measured by dynamic infusion cavernosometry, providing an objective measure of improved EF. Additional studies have found a variety of benefits with PDE5I administration in corporal nerve injured rats including reversing pro-fibrotic genes [51], decreasing apoptosis [52], decreased veno-occlusive dysfunction [50] and increased intracavernosal pressure [53, 54]. Taken as a whole, these findings form a strong basis for the rationale of use of PDE5Is in humans for penile rehabilitation.

Human Studies

Following Radical Prostatectomy

Several human studies in the last 15 years have demonstrated a potential beneficial effect of PDE5I use on recovery of EF following RP. In a 2004 study, Schwartz et al. randomized 40 patients with good preoperative EF to either 50 mg or 100 mg sildenafil every other night for 6 months following nerve-sparing RP [55]. A percutaneous biopsy of cavernosal tissue was taken at the time of surgery, as well as a second biopsy performed under local anesthesia at 6 months postoperatively. Postoperative smooth muscle content was compared to preoperative levels with those in the 100 mg group found to have significantly increased mean postoperative smooth muscle content (43 % vs. 57 %, $p<0.05$). However, smooth muscle content was found to be unchanged in the 50 mg group (52 % vs. 53 %, $p=0.81$).

To date, there have been four randomized, placebo controlled trials published that assesses the efficacy of PDE5Is in penile rehabilitation. Study designs are varied with some utilizing scheduled dosing only [56], on demand only [57] and a combination of scheduled and on demand drug [58, 59]. All studies show a benefit to the use of PDE5I in patients after nerve sparing RP although specific outcomes are variable. In the only studies looking at varied doses of PDE5I, no benefit was seen in a higher dose (100 mg of sildenafil vs. 50 mg of sildenafil) [56] while on demand dosing may have some benefits with an increasing dose [57].

Studies looking at a combination of scheduled and on demand dosing find contrary results although these could be somewhat dependent on

specifics of the drug involved. In their assessment of vardenafil, there was no different between on demand or scheduled dosing at the end of study period with the on demand dosing group having improvements in EF after washout and open label extension [58]. In a similarly designed study utilizing tadalafil instead, scheduled dosing had improvement over placebo for being a treatment responder (IIEF-EF>22) and mitigating penile length loss. The on demand dosing did not demonstrate these improvements over placebo, with the extended half life of tadalafil potentially accounting for these differences [59]. Table 20.1 summarizes the findings of the studies utilizing PDE5I in men after RP.

However, specific subgroups may benefit from rehabilitation with PDE5I differently and these large studies above may be too generalized to see the potential responders. In one study assessing patient characteristics to look for ideal responders, the group at "intermediate" risk for postoperative ED was considered the group to be the most likely to respond to this type of rehabilitation [60]. Conversely, the "low" risk group for post-RP ED are likely to recover as they have characteristics commensurate with good EF after surgery (better IIEF pre-op, younger age, less comorbidities) while patients at "high" risk for ED are unlikely to respond to rehabilitation due to already diminished function.

Following Radiotherapy

In a placebo-controlled trial on the efficacy of PDE5Is in the recovery of EF following radiotherapy, Zelefsky et al. examined the efficacy of daily sildenafil ollowing external beam radiotherapy (EBRT), brachytherapy, or combined brachytherapy and EBRT [61]. Therapy was started between 3 days prior to RT through 2 weeks after the first fraction of radiation or brachytherapy implantation and continued for 6 months. Twelve month follow-up results favored the sildenafil group, with significantly better IIEF-EF scores ($p=0.018$), as well as overall satisfaction scores ($p=0.027$). At the final study follow-up of 24 months, differences between groups in IIEF-EF ($p=0.172$) or overall IIEF ($p=0.09$) scores were no longer significant. However, overall satisfaction scores still favored the sildenafil group ($p=0.033$), as well as sexual desire scores ($p=0.049$). A similar, but smaller trial found no difference in EF with nightly sildenafil at 2 years or at any other point during the study [62].

It is possible that a longer course of penile rehabilitation would have maintained some of the benefits at 2 years in these studies, especially with the often delayed findings of ED in men treated with radiation. This thoughtful concept, in a group of largely undertreated men, will likely be reexamined in other studies utilizing different methodologies in the coming years.

Vacuum Erectile Device

Animal Studies

As a noninvasive and cost effective therapy, VED presents an attractive option for use in penile rehabilitation programs. Vacuum therapy utilizes negative pressure to distend corporal sinusoids and increase blood inflow. To test the effect of VED use after RP in an animal model, Yuan et al. randomized rats to bilateral cavernous nerve crush (BCNC), BCNC and VED therapy, or sham surgery [63]. After 4 weeks of treatment, the VED group was found to have significantly improved intracavernosal pressure with cavernous nerve stimulation as compared to the control groups. Further, the VED group demonstrated a significant reduction in apoptosis within corporal tissue. In a similar study, Lin et al. examined the effect of VED therapy on penile shortening and cavernosal oxygen saturation among rats that had underwent BCNC [64]. Results were promising, as the VED group was found to have no significant penile shortening compared to baseline, no reduction in penile circumference, and a significant increase in cavernosal oxygen saturation.

Human Studies

VED therapy trials have looked at outcomes in terms of EF, stretched penile length, and corporal oxygenation. There has been resurgence in VED use for ED [65] and the VED was the second most commonly used in a survey of AUA members [26].

Improvements in penile oxygen saturation with VED use has also been demonstrated in human studies. In a 2014 study, Welliver et al. recruited

Table 20.1 Summary of studies utilizing PDE5I in men after RP

Study	Groups	Primary outcomes	Secondary outcomes	Brief summary of study findings
Padma-Nathan et al. [56]	• Placebo QHS • Sildenafil 50 mg QHS • Sildenafil 100 mg Qhs	Percentage of patients who were drug "responders." Responders defined as having a combined score of at least 8 for Q3 and Q4 on the IIEF and also answered "yes" to "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?"	IIEF changes Duration of penile tumescence and rigidity.	More responders noted in the drug groups as compared to the placebo groups. No statistical increase in efficacy with higher dose of Sildenafil. At study end, IIEF scores were roughly 5 points higher in the drug groups. Patients had more penile rigidity in the drug groups.
Mulhall et al. [57]	• Placebo prn • Avanafil 100 mg prn • Avanafil 200 mg prn	Successful vaginal insertion (Sexual encounter profile [SEP] question 2), successful intercourse (SEP3), changes in IIEF-EF.	Changes in other domains on the IIEF, responses to diary questions, response to Global Assessment Question, response to future use question.	Improvements noted in SEP2 and SEP3 in drug groups but not placebo. Improvements of 3.6 (100 mg) and 5.2 (200 mg) in IIEF-EF. Drug groups had improvements in intercourse satisfaction and overall satisfaction when compared with placebo. Diary responses demonstrated increased sexual attempts where an erection was achieved and improved sexual experience.
Montorsi et al. [58]	• Placebo QHS/Placebo prn • Placebo QHS/Vardenafil prn • Vardenafil QHS/Placebo prn	Percentage of study subject with an IIEF-EF domain score ≥22 after the 2 month washout period.	Percentage of patients with IIEF-EF ≥ 22 at other study points. SEP2 and SEP 3 scores.	Only on demand Vardenafil was improved compared to placebo for primary outcome. On demand dosing was superior to nightly dosing at other points during the study. On demand Vardenafil was superior to both nightly dosing and placebo on SEP3 during double blind treatment period. Nightly Vardenafil was superior to placebo during this time period. Statistical differences between groups disappeared after washout.
Montorsi et al. [59]	• Placebo QHS/Placebo prn • Tadalafil 5 mg QHS/ Placebo prn • Placebo QHS/Tadalafil 20 mg prn	Proportion of study patients with an IIEF-EF score ≥22 after drug free washout period.	Secondary measures included. IIEF-EF, SEP3, and stretched penile length.	There was no difference in groups for the primary outcome. At the end of active drug treatment, daily Tadalafil had a larger percentage of patients with an IIEF-EF ≥22 when compared to placebo but not when compared to on demand Tadalafil. Penile length loss was mitigated by daily dosing only. Daily Tadalafil was superior to on demand Tadalafil and placebo at the end of treatment period with respect to SEP3 scores.

20 men with normal preoperative EF after bilateral nerve-sparing RP [66]. VED was applied in the clinic for maximum erection, and cycled for a 2 min period without use of a constriction ring. Penile oxygen saturation was measured with a tissue oximeter at baseline, immediately after VED use, and over the course of an hour. There was a statistically significant increase in corporal oxygen saturation of 55 % immediately after VED use. Oxygen saturation decayed over the study period, but remained significantly increased over baseline even at 60 min. The oxygenation effects with VED were somewhat similar to those found in men undergoing ICI [44].

Two randomized, controlled trials on VED therapy following RP have been conducted. Work by Kohler et al. demonstrated benefits in men who underwent both early (1 month following RP) or late (6 months after RP) rehabilitation with the VED [67]. At 3 months, IIEF scores were significantly higher in the early group ($p=0.008$), a difference which remained at 6 months ($p=0.012$). However, there were no differences between the groups with regards to EF at 12 months ($p=0.75$). Benefit was seen in early use of the VED with regards to stretched penile length, as those in the early group were less likely to have a mean length loss of greater than 2 cm (12 % vs. 45 %, $p=0.044$). An uncontrolled study looking at VED use after RP, found that in men using the device in more than 50 % of the first 90 days after surgery, only 3 % lost greater than 1 cm in stretched penile length [68]. A second RCT examining the VED found no differences in ability to achieve spontaneous erection, but men who underwent rehabilitation reported less difference in penile length and circumference in the postoperative period [69].

The one time fixed cost of the VED and relative ease of use over injection therapy makes this a convenient option for patients, even those who underwent non-nerve sparing RP. Efficacy has been noted in both corporal tissue oxygenation and reductions in penile shortening with less convincing outcomes with regards to improvements in EF. Patients who have not yet recovered continence may note leakage of urine when using the device for rehabilitation and should be warned of this before embarking on its use in rehabilitation protocols.

Psychosocial Interventions

While the above pharmacologic and mechanical interventions have shown efficacy, a more holistic approach including psychosocial interventions may also be of benefit. Counseling sessions with postoperative patients have shown increases in use of erectogenic aids [70], a decrease in dropouts from rehabilitation programs [71], and increased scores on objective measures of sexual function [70, 72]. While not large, or intensively constructed studies, they point towards a benefit for physiologic support in the postoperative period to augment the physical parts of penile rehabilitation.

Conclusion

Penile rehabilitation practices and protocols still vary widely and while many options exist, superiority has not been proven. This may be due to the overly general treatment plans supplied by physicians as individual patients may respond irregularly based on baseline sexual function, nerve sparing status, and personal preference. The physician instituting penile rehabilitation strategies after PC treatments needs to have a variety of treatment options in mind when counseling men on this problem.

References

1. Resnick MJ, Barocas DA, Morgans AK, Phillips SE, Koyama T, Albertsen PC, et al. The evolution of self-reported urinary and sexual dysfunction over the last Two decades: implications for comparative effectiveness research. Eur Urol. 2015;67(6):1019–25.
2. Prasad MM, Prasad SM, Hevelone ND, Gu X, Weinberg AC, Lipsitz SR, et al. Utilization of pharmacotherapy for erectile dysfunction following treatment for prostate cancer. J Sex Med. 2010;7(3):1062–73.

3. McCullough A, Levine LA, Padma-Nathan H. Return of nocturnal erections and erectile function after bilateral nerve-sparing radical prostatectomy in men treated nightly with sildenafil citrate: subanalysis of a longitudinal randomized double-blind placebo-controlled trial. J Sex Med. 2008;5:476–84.
4. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, Graefen M, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol. 2012;62:418–30.
5. Schover LR, Fouladi RT, Warneke CL, Neese L, Klein EA, Zippe C, et al. Defining sexual outcomes after treatment for localized prostate carcinoma. Cancer. 2002;95:1773–85.
6. Ganzer R, Blana A, Gaumann A, Stolzenburg JU, Rabenalt R, Bach T, et al. Topographical anatomy of periprostatic and capsular nerves: quantification and computerised planimetry. Eur Urol. 2008;54:353–60.
7. Takenaka A, Murakami G, Matsubara A, Han SH, Fujisawa M. Variation in course of cavernous nerve with special reference to details of topographic relationships near prostatic apex: histologic study using male cadavers. Urology. 2005;65:136–42.
8. Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderäng U, Thorsteinsdottir T, Lagerkvist M, Damber JE, Bjartell A, Hugosson J, Wiklund P, Steineck G, LAPPRO steering committee. Urinary incontinence and erectile dysfunction after robotic versus open radical prostatectomy: a prospective, controlled, nonrandomised trial. Eur Urol. 2015; 68(2):216–25.
9. van der Wielen GJ, Mulhall JP, Incrocci L. Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: a critical review. Radiother Oncol. 2007;84:107–13.
10. van der Wielen GJ, Vermeij M, de Jong BW, Schuit M, Marijnissen J, Kok DJ, van Weerden WM, Incrocci L. Changes in the penile arteries of the rat after fractionated irradiation of the prostate: a pilot study. J Sex Med. 2009;6:1908–13.
11. Zelefsky MJ, Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostatic cancer. Int J Radiat Oncol Biol Phys. 1998;40:129–33.
12. Goldstein I, Feldman MI, Deckers PJ, Babayan RK, Krane RJ. Radiation-associated impotence. A clinical study of its mechanism. JAMA. 1984;251:903–10.
13. Hall SJ, Basile G, Bertero EB, de las Morenas A, Goldstein I. Estensive corporeal fibrosis after penile irradiation. J Urol. 1995;153:372–7.
14. Carrier S, Hricak H, Lee SS, Baba K, Morgan DM, Nunes L, Ross GY, Phillips TL, Lue TF. Radiation-induced decrease in nitric oxide synthase—containing nerves in the rat penis. Radiology. 1995;195:95–9.
15. Mulhall J, Ahmed A, Parker M, Mohideen N. The hemodynamics of erectile dysfunction following external beam radiation for prostate cancer. J Sex Med. 2005;2:432–7.
16. Bushberg, Jt. Radiation Exposure and Contamination. In Merck Manual Online. Retrieved at http://www.merckmanuals.com/professional/injuries_poisoning/radiation_exposure_and_contamination/radiation_exposure_and_contamination.html
17. van der Wielen GJ, Hoogeman MS, Dohle GR, van Putten WL, Incrocci L. Dose-volume parameters of the corpora cavernosa do not correlate with erectile dysfunction after external beam radiotherapy for prostate cancer: results from a dose-escalation trial. Int J Radiat Oncol Biol Phys. 2008;71:795–800.
18. Merrick GS, Butler WM, Galbreath RW, Stipetich RL, Abel LJ, Lief JH. Erectile function after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2002;52:893–902.
19. Ong WL, Hindson BR, Beaufort C, Pharoah P, Millar JL. Long-term erectile function following permanent seed brachytherapy treatment for localized prostate cancer. Radiother Oncol. 2014;112:72–6.
20. Litwin MS, Flanders SC, Pasta DJ, Stoddard ML, Lubeck DP, Henning JM. Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaPSURE. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology. 1999;54:503–8.
21. Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, Harlan LC. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst. 2004;96(18):1358–67.
22. Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368:436–45.
23. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med. 2009; 6:2538–46.
24. Briganti A, Gallina A, Suardi N, Capitanio U, Tutolo M, Bianchi M, et al. What is the definition of a satisfactory erectile function after bilateral nerve sparing radical prostatectomy? J Sex Med. 2011;8:1210–7.
25. Giuliano F, Amar E, Chevallier D, Montaigne O, Joubert JM, Chartier-Kastler E. How urologists manage erectile dysfunction after radical prostatectomy: a national survey (REPAIR) by the French urological association. J Sex Med. 2008;5:448–57.
26. Tal R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. J Sex Med. 2011;8(8):2370–6.
27. Teloken P, Mesquita G, Montorsi F, Mulhall J. Post-radical prostatectomy pharmacological penile rehabilitation: practice patterns among the international society for sexual medicine practitioners. J Sex Med. 2009;6(7):2032–8.
28. Muller A, Parker M, Waters BW, Flanigan RC, Mulhall JP. Penile rehabilitation following radical prostatectomy: predicting success. J Sex Med. 2009; 6(10):2806–12.
29. Gallina A, Ferrari M, Suardi N, Capitanio U, Abdollah F, Tutolo M, et al. Erectile function outcome after

bilateral nerve sparing radical prostatectomy: which patients may be left untreated? J Sex Med. 2012;9(3):903–8.
30. Briganti A, Gallina A, Suardi N, Capitanio U, Tutolo M, Bianchi M, et al. Predicting erectile function recovery after bilateral nerve sparing radical prostatectomy: a proposal of a novel preoperative risk stratification. J Sex Med. 2010;7(7):2521–31.
31. Rabbini F, Stapleton AM, Kattan MW, Wheeler TM, Scardino PT. Factors predicting recovery of erections after radical prostatectomy. J Urol. 2000;164:1929–34.
32. Alemozaffar M, Regan MM, Cooperberg MR, Wei JT, Michalski JM, Sandler HM, et al. Prediction of erectile function following treatment for prostate cancer. JAMA. 2011;306:1205–14.
33. Ko WJ, Truesdale MD, Hruby GW, Landman J, Badani KK. Impacting factors for recovery of erectile function within 1 year following robotic-assisted laparoscopic radical prostatectomy. J Sex Med. 2011;8(6):1805–12.
34. Moskovic DJ, Alphs H, Nelson CJ, Rabbani F, Eastham J, Touijer K, et al. Subjective characterization of nerve sparing predicts recovery of erectile function after radical prostatectomy: defining the utility of a nerve sparing grading system. J Sex Med. 2011;8(1):255–60.
35. Michl UH, Friedrich MG, Graefen M, Haese A, Heinzer H, Huland H. Prediction of postoperative sexual function after nerve sparing radical retropubic prostatectomy. J Urol. 2006;176:227–31.
36. User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol. 2003;169(3):1175–9.
37. Iacono F, Giannella R, Somma P, Manno G, Fusco F, et al. Histological alterations in cavernous tissue after radical prostatectomy. J Urol. 2005;173(5):1673–6.
38. Mulhall JP, Parker M, Waters BW, Flanigan R. The timing of penile rehabilitation after bilateral nerve-sparing prostatectomy affects the recovery of erectile function. BJU Int. 2010;105(1):37–41.
39. Mosbah A, El Bahnaway M, Osman Y, Hekal IA, Abou-Beih E, et al. Early versus late rehabilitation of erectile function after nerve-sparing radical cystoprostatectomy: a prospective randomized study. J Sex Med. 2011;8(7):2106–11.
40. Gontero P, Fontana F, Bagnasacco A, Panella M, Kocjancic E, et al. Is there an optimal time for intracavernous prostaglandin E1 rehabilitation following nonnerve sparing radical prostatectomy? Results from a hemodynamic prospective study. J Urol. 2003;169:2166–9.
41. Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol. 1997;158:1408–10.
42. Yiou R, Cunin P, de la Taille A, et al. Sexual rehabilitation and penile pain associated with intracavernous alprostadil after radical prostatectomy. J Sex Med. 2011;8:575–82.
43. Montague DK, Jarow JP, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, et al. Chapter 1: the management of erectile dysfunction: an AUA update. J Urol. 2005;174(1):230–9.
44. Padmanabhan P, McCullough AR. Penile oxygen saturation in the flaccid and erect penis in men with and without erectile dysfunction. J Androl. 2007;28:223–8.
45. McCullough AR, Hellstrom WG, Wang R, Lepor H, Wagner KR, et al. Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus sildenafil citrate. J Urol. 2010;183:2451–6.
46. Raina R, Pahlajani G, Agarwal A, Zippe CD. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. BJU Int. 2007;100:1317–21.
47. Mydlo JH, Volpe MA, MacChia RJ. Results from different patient populations using combined therapy with alprostadil and sildenafil: predictors of satisfaction. BJU Int. 2000;86(4):469–73.
48. Nehra A, Blute ML, Barrett DM, Moreland RB. Rationale for combination therapy of intraurethral prostaglandin E(1) and sildenafil in the salvage of erectile dysfunction patients desiring noninvasive therapy. Int J Impot Res. 2002;14 Suppl 1:S38–46.
49. Mulhall J, Land S, Parker M, Waters WB, Flanigan RC. The use of an erectogenic pharmacotherapy regimen following radical prostatectomy improves recovery of spontaneous erectile function. J Sex Med. 2005;2(4):532–40. discussion 40-2.
50. Ferrini MG, Davila HH, Kovanecz I, Sanchez SP, Gonzalez-Cadavid NF, et al. Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. Urology. 2006;68(2):429–35.
51. Sirad F, Hlain S, Kovanecz I, Artaza JN, Garcia LA, et al. Sildenafil promotes smooth muscle preservation and ameliorates fibrosis through modulation of extracellular matrix and tissue growth factor gene expression after bilateral cavernosal nerve resection in the rat. J Sex Med. 2011;8:1048–60.
52. Lysiak JJ, Yang S, Klausner AP, Son H, Tuttle JB, et al. Tadalafil increases Akt and extracellular signal-regulated kinase ½ activation, and prevents apoptotic cell death in the penis following denervation. J Urol. 2008;179:779–85.
53. Kovanecz I, Rambhatla A, Ferrini MG, et al. Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. BJU Int. 2008;101:203–10.
54. Mulhall JP, Muller A, Donohue JF, et al. The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. J Sex Med. 2008;5:1126–36.
55. Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. J Urol. 2004;171:771–4.

56. Padma-Nathan H, McCullough AR, Levine LA, Lipshultz LI, Siegel R, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res. 2008;20:479–86.
57. Mulhall JP, Burnett AL, Wan R, McVary KT, Moul JW. A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. J Urol. 2013;189:2229–36.
58. Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, Graefen M, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54:924–31.
59. Montorsi F, Brock G, Stolzenburg J, Mulhall J, Moncada I, Patel HR, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomized placebo-controlled study (REACTT). Eur Urol. 2014; 65:587–96.
60. Briganti A, Di Trapani E, Abdollah F, Gallina A, Suardi N, Capitanio U, et al. Choosing the best candidates for penile rehabilitation after bilateral nerve-sparing radical prostatectomy. J Sex Med. 2012; 9(2):608–17.
61. Zelefsky MJ, Shasha D, Branco RD, Kollmeier M, Baser RE, et al. Prophylactic sildenafil citrate improves select aspects of sexual function in men treated with radiotherapy for prostate cancer. J Urol. 2014;192:868–74.
62. Ilic D, Hindson B, Duchesne G, Millar JL. A randomised, double-blind, placebo controlled trial of nightly sildenafil citrate to preserve erectile function after radiation treatment for prostate cancer. J Med Imaging Radiat Oncol. 2013;57:81–8.
63. Yuan J, Lin H, Li P, Zhang R, Luo A, et al. Molecular mechanisms of vacuum therapy in penile rehabilitation: A novel animal study. Eur Urol. 2010;58:773–80.
64. Lin H, Yang W, Zhang J, Dai Y, Wan R. Penile rehabilitation with a vacuum erectile device in an animal model is related to an antihypoxic mechanism: blood gas evidence. Asian J Androl. 2013;15:387–90.
65. Brison B, Seftel A, Sadeghi-Nejad H. The resurgence of the vacuum erection device (VED) for the treatment of erectile dysfunction. J Sex Med. 2013;10: 1124–35.
66. Welliver Jr RC, Mechlin C, Goodwin B, Alukal JP, McCullough AR. A pilot study to determine penile oxygen saturation before and after vacuum therapy in patients with erectile dysfunction after radical prostatectomy. J Sex Med. 2014;11:1071–7.
67. Kohler TS, Pedro R, Hendlin K, Utz W, Ugarte R, et al. A pilot study on the early use of the vacuum erectile device after radical retropubic prostatectomy. BJU Int. 2007;100:858–62.
68. Dalkin BL, Christopher BA. Preservation of penile length after radical prostatectomy: early intervention with a vacuum erection device. Int J Impot Res. 2007;19:501–4.
69. Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. Int J of Impotence Res. 2006;18:77–81.
70. Canada AL, Neese LE, Sui D, Schover LR. Pilot intervention to enhance sexual rehabilitation for couples after treatment for localized prostate carcinoma. Cancer. 2005;104:1689–2700.
71. Titta M, Tavolini IM, Dal Moro F, Cisternino A, Bassi P. Sexual counseling improved erectile rehabilitation after non-nerve-sparing radical retropubic prostatectomy or cystectomy—results of a randomized prospective study. J Sex Med. 2006;3(2):267–73.
72. Molton IR, Siegel SD, Penedo FJ, et al. Promoting recovery of sexual functioning after radical prostatectomy with group-based stress management: the role of interpersonal sensitivity. J Psychosom Res. 2008;64: 527–36.

Peyronie's Disease: Natural History, Diagnosis, and Medical Therapy

21

James R. Craig, William O. Brant, James F. Smith, and Tom F. Lue

Introduction

François Gigot de la Peyronie (Fig. 21.1), surgeon to King Louis XV of France, is given credit for first describing penile curvature in 1743; however, older accounts from Fallopius have been found from 1561 [1]. Peyronie's disease, also known as induratio penis plastica, is described as penile curvature which may be associated with painful erections and a palpable plaque. This chapter concentrates on the natural history, epidemiology, diagnostic evaluation, and medical therapy for Peyronie's disease. The surgical management of Peyronie's disease is discussed in a different chapter (Chap. 23).

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Natural History

Epidemiology

The reported prevalence of Peyronie's disease is quite variable ranging from 0.4 % [2] to 23 % from a cadaveric study [3]. More recent studies have provided a better idea of the true prevalence of Peyronie's disease. A population based study from Cologne, Germany [4], illustrated a rate of Peyronie's disease of 3.2 %. They noted a rising incidence based on increasing age: 1.5 % of the men between the ages of 30 and 39 and 6.5 % of the men over the age of 70. Two other groups in Brazil and the USA found a rate of 3.6 % [5] and 8.9 % [6] respectively of Peyronie's disease in men presenting for prostate cancer screening. The findings of these studies are in contrast to a 0.6 % prevalence rate reported in a Japanese population undergoing routine health checks [7] potentially suggesting variable rates of Peyronie's disease based on ethnicity versus variable differences due to how Peyronie's disease is defined.

Although the true incidence of Peyronie's disease is not exactly known, it is not the rare entity it was once felt to be. Peyronie's disease

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Fig. 21.1 François Gigot de la Peyronie, surgeon to King Louis XV of France. (Source: BIU Santé (Paris)/http://www.biusante.parisdescartes.fr/histmed/image?CIPB0999.)

has been found to affect a broad range of age groups, and is more commonly seen in the older population.

Etiology

To better understand Peyronie's disease we must review the anatomical and physiological factors involved. Lue et al. compared micrographs of normal penile tissue to penile tissue with Peyronie's disease in cadavers. In the normal penile tissue the tunica albuginea was not composed of a single layer as once thought, but of multiple layers of predominantly type 1 collagen. The outer layers are oriented in a longitudinal fashion and the inner layer is oriented in a circular fashion with pillar-like

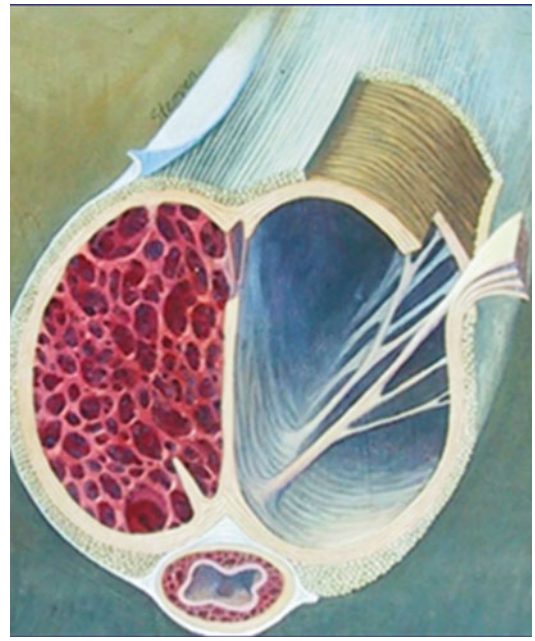

Fig. 21.2 Penile cross section

extensions acting as struts which are attached at the septum (Fig. 21.2). In the Peyronie's disease penises this uniform architecture of collagen was found to be disrupted and replaced by nodular like clumps of type III collagen [8]. Calcification of the plaque may also occur and has been demonstrated in a third of patients presenting with Peyronie's disease [9].

The physiological mechanism by which fibrosis of the tunic albuginea occurs is likely related to the persistent presence of myofibroblasts and its subsequent production of TGFβ1 and fibrin followed by abnormal collagen deposition and plaque formation. Interestingly, on evaluation of these plaques increased levels of inducible nitric oxide (iNOS) and nitric oxide have been found. Both nitric oxide and its product cGMP have been found to induce myofibroblasts apoptosis and resultant decreased plaque size. These findings suggest a persistent pro-fibrotic and antifibrotic process which occurs in the plaque and gives us insight into potential targeted therapies for Peyronie's disease [10, 11].

The inciting event leading to Peyronie's disease is thought to be related to microtrauma which causes delamination of the layers of the tunica

albuginea and separation of the struts from the inner layer of the tunica albuginea. This focal area of edema leads to compression of venous outflow allowing for the accumulation of pro-inflammatory substances. This inflammatory response is what likely leads to localized pain [12].

For this theory of trauma as the inciting event which leads to Peyronie's disease to hold true we should see an equal rate of disease across all ages of sexually active men and potentially an increased frequency in age groups who are more sexually active. However, this is not what has been reported in multiple population based studies which show an increased incidence of Peyronie's disease in the older population [4]. One suggested theory is that less rigid erections, which may be seen in an older population, leads to increased buckling forces and increased risk of trauma. The tunica albuginea in older individuals may also have less elastin fibers leading to an increased risk of the layers of the tunica albuginea becoming disrupted. Other risk factors which place individuals at an increased risk of having Peyronie's disease and are more likely to be seen in the aging population include diabetes mellitus, beta blocker/thiazide diuretic use, LDL >130, (likely acting as a surrogate for cardiovascular disease and thus erectile dysfunction), history of Dupuytren's contracture, and Caucasian race [4, 13]. Current use of hemodialysis has also been demonstrated as an independent risk factor of developing Peyronie's disease [7].

To evaluate different presenting factors which are dependent upon age, Mulhall's group [14] described a group of men presenting with Peyronie's disease and separated them between men less than 40 years of age and men greater than 40 years of age. They found that men less than 40 years of age were more likely to present with pain, have multiple plaques, and have a history of penile trauma. Men greater than 40 years of age were more likely to have a longer history of disease (2 months < 40 years of age and 6 months > 40 years of age), were more likely to present with penile curvature, and have a history of Dupuytren's contracture.

Individuals being evaluated for erectile dysfunction are more likely to have concomitant findings of Peyronie's disease. An Italian group reported a rate of Peyronie's disease in this population at 10 %. They also demonstrated and increased rate of Peyronie's disease in individuals greater than 40 years of age versus less than 40 years of age, 11.4 % versus 4.4 % respectively. They again confirmed increased rate of concomitant findings of cardiovascular disease including hypertension and hyperlipidemia in the older age group [15]. A second group from Iran reported a rate of Peyronie's disease in 8.1 % of men with diabetes. They also found an increased rate of Peyronie's disease in their population when diabetes was considered to be poorly controlled and there was a history of diabetes greater than 10 years [16].

Other groups with higher incidence of Peyronie's disease include individuals who have undergone a prostatectomy. Mulhall's group [17] described a group of men after radical prostatectomy with new penile curvature after surgery as having a 15.9 % rate of Peyronie's disease.

Diagnosis

Clinical Manifestation

Presenting symptoms of Peyronie's disease are attributed to the pathophysiology of the disease process. Symptoms have been differentiated into two groups, acute phase and chronic. Acute phase include penile pain, plaque, and evolving deformity. Chronic symptoms include minimal/no pain, plaque, and stable penile deformity. The classic triad of palpable plaque, penile deformity, and pain with erection were only reported by 32 % of the affected individuals [4]. Other symptoms of Peyronie's disease include erectile dysfunction and loss of penile length [18].

The rate of penile pain, plaque, and deformity alone or accompanied with other symptoms varies from 14 % to 47 % [4, 14, 19, 20], 13 % to 84 % [4, 20], and 73 % to 75 % [19, 20], respectively.

The location and extent of the plaque is the cause of penile deformities seen with Peyronie's disease. A general rule of thumb is that the erect penis will

curve in the direction of the plaque leading to dorsal, ventral, and lateral curvature. Other less common and more complex forms of curvature include corkscrew, notching, and hourglass. The location of the penile plaque varies but is most commonly present at the dorsal penis 30–45 % followed by the lateral aspect 29–38 % [19, 20].

Difficulty with penile insertion may be described by patients and should be differentiated from loss of penile rigidity (erectile dysfunction) and severe penile curvature making penetration difficult. Erectile dysfunction has been reported from 15 to 70 % from individuals being evaluated for Peyronie's disease [19–21].

There is also a significant amount of psychological distress which stems from Peyronie's disease. Mulhall's group demonstrated a significant rate of depression, 48 %, in individuals with Peyronie's disease which remained constant over time after initial diagnosis for these individuals [22]. Lue's group [23] also reported a large number of men with self-reported emotional and relationship problems which were associated with Peyronie's disease.

Physical Examination

A detailed genital examination is necessary in the individual with Peyronie's disease in order to accurately counsel patients on disease severity and offer appropriate treatment modalities. It is also important to accurately document these findings in order better evaluate outcomes after treatment. Key points in the physical examination include assessment in stretched penile length and defining plaque characteristics (location, size, pain on palpation, texture, and number).

Erectile function should also be assessed. This is typically performed with the use of a validated questionnaire such as Sexual Health Inventory for Men (SHIM). More recently the Peyronie's Disease Questionnaire (PDQ) has been validated [24]. It contains three domains specific to Peyronie's disease, and these are: (1) psychological and physical symptoms; (2) penile pain; and (3) symptom bother. This questionnaire has been largely utilized in two Phase 3 trials of collagenase clostridium histolyticum for Peyronie's disease where it has been shown to be highly responsive to change in men undergoing this treatment for Peyronie's disease [25].

The degree of penile curvature upon erection should be established on evaluation. Patient reported degree of penile curvature is largely inaccurate, with overestimation up to 20° being the most common [26]. Other methods of assessing penile curvature include patient supplied photographs of their maximally erect phallus from both the dorsal and lateral aspects. For patients who have complaints of erectile dysfunction they may be unable to supply sufficient information to determine penile curvature. In these instances it may be warranted to proceed with intracavernosal injection of erectogenic medications. This allows assessment of both penile curvature as well as potential evaluation of the etiology of erectile dysfunction with penile color duplex ultrasound.

Diagnostic Imaging Studies

Painful penile indurations or palpable penile plaques/masses warrant imaging in addition to physical examination. Although the majority of these individuals will have Peyronie's disease [27, 28], other non-malignant and malignant etiologies of these symptoms should be ruled out. Imaging modalities which have been utilized to evaluate individuals with suspicion of Peyronie's disease include ultrasound, CT, MRI, and X-ray. Penile ultrasound has been shown to be more useful in measuring tunica albuginea thickness, presence of calcifications, and fibrosis of the corpora cavernosa and septum [29–31]. Techniques for penile ultrasound may vary; however, generally involve the use of B-mode imaging with a small-parts linear probe set at high frequency (>10 MHz). With the phallus in the flaccid status it is probed in its entire accessible length in both the longitudinal and transverse planes. In patients with complaints of erectile dysfunction color duplex ultrasonography should be performed again with the phallus in the erect state which is achieved via intracavernosal injection of an erectogenic medication.

Key findings on B-mode ultrasound include presence of calcification, septal fibrosis, intracavernosal fibrosis, and tunica albuginea fibrosis. Lue's group [9] described a group of 528 men with Peyronie's disease who were evaluated with penile ultrasound. The most common finding was thickening of the tunica albuginea at 50 % followed by calcifications at 31.4 %, septal fibrosis at 19.9 %, and intracavernosal fibrosis at 15 %. Only 0.8 % of these individuals manifest all four findings. When these ultrasound findings were associated with disease characteristics they were all found to have different and significant Peyronie's disease clinical characteristics (penile pain, ability to have intercourse, loss of penile length, and penile curvature). The presence of septal fibrosis was more commonly seen in younger men (less than 40 years of age) and significantly less likely to be seen in conjunction with other medical comorbidities including hypertension, diabetes mellitus, and coronary artery disease. This is in contrast to the finding of calcifications which was more likely to be seen in older men (greater than 40 years of age) and in men with a history of diabetes mellitus. Thickening of the tunica albuginea was found to be significantly more common in individuals greater than 50 years of age and was also significantly associated with a history of inability to have sexual intercourse and were less likely to have a history of penile injury. Presence of intracavernosal fibrosis was not associated with age, medical comorbidities, or history of trauma. However, it was significantly associated with difficulty with intercourse, penile deformity, and rapid onset of disease.

Erectile dysfunction as a component of Peyronie's disease is related to both structural abnormalities as well as hemodynamic abnormalities. For this reason it is important to utilize color duplex ultrasonography to evaluate for hemodynamic abnormalities. Kadioglu et al. [21] evaluated a cohort of men with Peyronie's disease with color duplex ultrasound and separated then men into two groups, those with erectile dysfunction and those without erectile dysfunction. They found than 76 % in their total group of patients had some form of vascular abnormality with the most common being veno-occlusive dysfunction (defined as a peak end diastolic velocity greater than 5 cm/s). However, arterial insufficiency (defined as a peak systolic velocity less than 35 cm/s) was only seen in the group with erectile dysfunction. From a pure penile vascular standpoint, erectile dysfunction in individuals with Peyronie's disease is most likely resultant from a combination of veno-occlusive dysfunction and arterial insufficiency.

Appropriately identifying and defining the extent of penile lesions on ultrasound is important as this may offer some prognostic information for the patient and to serve as a guide for the treating urologist to be more comfortable with offering observation or treatment. A group from Greece [32] evaluated a cohort of patients with Peyronie's disease over a year with penile ultrasound performed at initial evaluation and at the end of the 1 year follow-up. They found that 81 % of men with a single small (0.4–1.9 cm) hyperechoic lesion (suggestive of tunica albuginea fibrosis) had improvement in the size of the lesion as well as improvement in their penile curvature. The second two groups in this study, those with multiple moderately hyperechoic scattered calcified lesions and those with a dense calcified hyperechoic plaque were shown to have a 34 and 0 % chance in improvement in plaque size and penile curvature. Over 50 % of those individuals with multiple small calcified lesions were noted to progress to a dense calcified plaque. The identification of calcifications is important as this has been shown to be a predictive finding on penile ultrasound for proceeding to surgical correction of Peyronie's disease [33].

Medical Therapy

No unified algorithm exists for the medical therapy of Peyronie's disease and until recently there were no FDA approved therapies. The majority of therapies target specific mechanisms in plaque formation such as inflammation, cell proliferation of myofibroblasts, production of free radicals, and oxidants. These targeted therapies primarily are administered via an oral route with a select few

introduced directly into the plaque via injection or superficial to the plaque via a topical agent. Other therapies are directed at disrupting the plaque either by mechanical forces or by injecting a dissolving agent into the plaque. Collagenase clostridium histolyticum (Xiaflex® Auxilium Pharmaceuticals/Endo Pharmaceuticals, Dublin, Ireland) is currently the only FDA approved therapy for Peyronie's disease and is used as an intralesional injection therapy directed towards dissolving the collagen within the plaque. Below is a list of these therapies categorized by route of administration. We also discuss literature regarding their efficacy in the management of Peyronie's disease.

Oral Therapy

Vitamin E

Although numerous in vitro studies have demonstrated the potent antioxidant properties of vitamin E (alpha-tocopherol) [34, 35], these properties may not translate into improved clinical outcomes for men with PD [35]. Several randomized studies have shown no benefit [36, 37]; however, when vitamin E was combined with colchicine, a single-blind, small randomized controlled trial in men with mild, early PD demonstrated significantly decreased plaque size in the intervention arm [38]. Despite this lack of efficacy, vitamin E is often prescribed because of its ease of use and the perception of few side effects. Unfortunately, a growing body of literature suggests a possible link between chronic, high dose vitamin E ingestion and significant side effects such as increased heart failure, blood pressure, and all-cause mortality; however, these findings were confined to patients being treated for chronic medical conditions, such as diabetes, cardiovascular disease, and hypertension [39].

L-Carnitine

L-Carnitine increases mitochondrial respiration and decreases free radical formation thus suggesting a mechanism of action to treat PD [40]; however, data from randomized trials have been equivocal. When combined with intralesional verapamil, L-carnitine significantly decreased penile curvature and plaque size relative to verapamil injections and oral tamoxifen [41]. Another trial comparing tamoxifen to L-carnitine demonstrated decreased plaque size and curvature in the L-carnitine arm and found that L-carnitine provided significant pain reduction and fewer side effects than tamoxifen [42]. Conversely, a larger trial comparing vitamin E and L-carnitine to vitamin E alone did not demonstrate significant clinical benefit [37]. Side effects are usually mild but include mild euphoria [42] and gastrointestinal upset with doses greater than 4 g/day [43].

Potassium Para-Aminobenzoate (Potaba®)

Potaba® (Glenwood, LCC, Englewood, NJ) (potassium paraaminobenzoate) may exert its effects through anti-inflammatory and antifibrotic mechanisms. Several observational studies have demonstrated its effectiveness in treating PD [44, 45]. In the lone clinical trial conducted, men randomized to the Potaba® arm, all of whom had early-stage PD, had a greater reduction in plaque size [46]. Despite the limited data, Potaba® holds promise in terms of stabilizing preexisting lesions and preventing new plaques from forming; however, frequent dosing, significant gastrointestinal side effects and its relatively high cost limit its use.

Pentoxifylline

Pentoxifylline is a nonspecific PDE-5 inhibitor with anti-inflammatory properties used to treat claudication and symptomatic cerebral atherosclerosis [47], kidney transplants, open heart surgery, dermatologic conditions, and radiation-induced fibrosis as a means of decreasing inflammation and fibrosis [48–52]. The potential benefit of pentoxifylline for the treatment of PD is based upon data from in vitro and in vivo models. Pentoxifylline added to fibroblast culture resulted in an up regulation of cAMP and decreased collagen I production [53]. These researchers also demonstrated decreased levels of profibrotic factors and decreased size of fibrotic plaques after the treatment with pentoxifylline in a rat model of Peyronie's disease. Additional in vitro evidence revealed an upregula-

tion of osteoclastic activity after the treatment with pentoxifylline [54].

From a clinical standpoint, case reports suggest that pentoxifylline may prevent corporal fibrosis after priapism [55] and decrease calcifications in new-onset Peyronie's disease [56]. The reduction in tunica albuginea calcifications may derive from pentoxifylline's ability to promote osteoclastic activity. In general, side effects are mild and consist of nausea, dizziness, and headache [34]. Despite the potential for benefit based upon its mechanism of action and early clinical data, higher quality data are needed to support the use of pentoxifylline for the routine treatment of PD.

Tamoxifen

Tamoxifen, a nonsteroidal antiestrogen, may reduce the production of TGF-β by fibroblasts in the tunica albuginea [57]. Observational studies have demonstrated modest treatment benefits [58]. One clinical trial revealed no significant difference between tamoxifen and placebo [59], while another found that tamoxifen was inferior to L-carnitine in terms of reducing penile curvature and pain, and plaque size during the early stage of PD [42].

Colchicine

Colchicine is often used for the treatment of gout and a variety of malignancies [59, 60] and has been used for the treatment of PD because of its anti-inflammatory properties. One randomized study has shown decreased plaque size in the acute phase of PD [38]; however, these findings could not be repeated in a subsequent, larger clinical trial [60]. Because of the potential for significant bone marrow suppression, a complete blood count should be obtained quarterly. More commonly, gastrointestinal side effects (i.e., diarrhea, nausea, and anorexia) are reported [34].

Phosphodiesterase Type 5 Inhibitors

Several studies have reported expression of inducible nitric oxide synthase (iNOS) within penile plaques which in turn leads to increased production of nitric oxide and cGMP. These products exert an antifibrotic effect in the penile plaque and potentially have a role in plaque stabilization or resolution [10, 61, 62]. Phosphodiesterase type 5 inhibitors have been utilized in the management of these fibrotic penile plaques based on these findings. A Canadian group described a group of men with septal fibrosis and erectile dysfunction who were managed with tadalafil 2.5 mg daily versus no treatment and followed them with penile ultrasound. They noted a significant improvement in IIEF score in the treatment group as well as resolution in septal scarring in 69 % in the treatment group versus 10 % in the non-treatment group which was significant in a 6 month period [63].

Intralesional Therapy

Verapamil

Intralesional injection of calcium channel blockers, such as verapamil, has been shown to decrease plaque size and penile curvature. They function by inhibiting the production of extracellular matrix proteins and decreasing the production of TGF-β and collagen. Oral verapamil therapy is not utilized because effective oral doses produce serum levels 100-fold greater than the toxic threshold [64, 65]. Several randomized trials have demonstrated improvements in penile curvature, and erectile function, as well as decreased plaque size after the treatment with intralesional verapamil [41, 65, 66]; however, a recent systematic review highlighted many methodological weaknesses that limit the strength of conclusions about the effectiveness of intralesional verapamil [67]. Further, this mode of delivery can only be successful for palpable lesions.

Interferon Alpha-2b

As abnormalities in collagen deposition and composition of the tunica albuginea appear to underlie a significant portion of the plaques observed in PD, the discovery that in vitro administration of interferon α-2b (IFN-α) decreased the production of extracellular matrix collagen and increased collagenase in fibroblasts derived from Peyronie's plaques provided evidence that this could be an effective treatment [68, 69]. A small randomized study with three study arms comparing IFNα-2b

in combination with vitamin E to IFNα-2b alone or vitamin E alone did not demonstrate benefit with intralesional IFNα-2b in combination with vitamin E over the 6-month study period [36, 70]. In contrast, a nonrandomized, non-blinded, prospective cohort study did show a significant decrease in curvature and plaque size in men treated with intralesional IFN-α [70]. Other explanations, such as patient age or selection of participants, medical comorbidities, and duration of disease, might have contributed to the significant findings in this study. The administration of IFN-α is commonly associated with flu-like symptoms (fever, chills, and arthralgias), minor penile swelling, and sinusitis; however, these resolved spontaneously within 36 h of treatment with over-the-counter nonsteroidal anti-inflammatory medication.

Collagenase Clostridium Histolyticum

The use of a collagenase as an intralesional injection agent in the treatment of Peyronie's disease has been described for over two decades [71–73]. Xiaflex® (Auxilium Pharmaceuticals/Endo Pharmaceuticals, Dublin, Ireland), which is composed of two forms of collagenase clostridium histolyticum (AUX-1 and AUX-2), was recently approved by the FDA for use in the treatment of Peyronie's disease after the completion of two large double-blind, randomized, placebo controlled Phase 3 trials evaluating the clinical efficacy, safety, and tolerability of collagenase clostridium histolyticum were published in 2013 [74]. Men enrolled in these studies were grouped into two arms: collagenase with penile modeling and placebo with penile modeling. The injections consisted of four treatment cycles each of which were separated by 6 weeks. Each cycle consisted of an injection followed by a second injection 24–72 h later followed by penile modeling 72 h later. Individuals who received collagenase received 0.58 mg of collagenase. Those in the collagenase group were found to have a significant improvement in the degree of penile curvature of 38 % (17° improvement) compared to the placebo group who experienced an improvement of 18 % (9° improvement). Study enrollees were also administered the Peyronie's Disease Questionnaire prior to and after competition of the study. Those who were administered the collagenase were noted to have a significant improvement in all parameters of the questionnaire except penile length and penile pain when compared to the placebo group. Adverse events were primarily seen in the collagenase group with the most common events being penile ecchymosis, penile swelling, and penile pain. There were six serious adverse events including three men who experienced corporal rupture and three men who experienced penile hematoma. Antibody development to AUX-1 and AUX-2 occurred in 99 % of individuals by the end of the study without report of immunological event.

Iontophoresis

Superoxide Dismutase (Orgotein, Lipoxysan® (Polymun Scientific Immunbiologische Forschung GmbH, Austria))

Collagen abnormalities observed in the tunica albuginea of men with PD may result from the effects of inflammation with subsequent development of oxygen free radicals. This theory has led to the successful use of superoxide dismutase, a potent scavenger of oxygen free radicals, to decrease the inflammation associated with PD [75, 76] and theoretically offers benefit for inflammatory lesions associated with PD. In spite of this theory, a small clinical trial did not demonstrate convincing evidence of therapeutic benefit [77]. A later small, clinical trial using human recombinant superoxide dismutase revealed significantly greater pain relief among treated men [78].

Verapamil

Electromotive verapamil therapy (EMDA) with dexamethasone can significantly decrease penile curvature and plaque size relative to a lidocaine control [79]. Spontaneous resolution of mild erythema at the electrodes site was observed and no other significant side effects were noted. Contrary to these results, a recent randomized, controlled trial of men treated twice weekly with EMDA for 3 months did not reveal a significant

clinical improvement [80]. The primary benefit of utilizing EMDA as a drug delivery mechanism arises from the ease of application and minimal side effects.

Topical Verapamil

A double-blind, placebo controlled study evaluating topical verapamil hydrochloride applied twice daily over the entire shaft of the penis resulted in a significant reduction in curvature, plaque size, and improvements in erectile function after 3 months of treatment [81]. This study also assessed the effect of topical verapamil relative to the calmodulin-blocker, trifluoperazine, and placebo. Several methodological flaws compromise the quality of this data and weaken conclusions that can be drawn from it. Further, it was found that trifluoperazine had significant side effects, including anxiety, agitation, blurred vision, insomnia, and depression. While these results suggest a benefit, additional doubt about the effectiveness of this treatment arises from controversy about the ability of topical verapamil to truly penetrate the tunica albuginea [82].

Other Nonsurgical Treatments

Penile Traction

Two recent studies have reported promising results for penile traction therapy as an adjunct to oral and intralesional therapy for PD. One small observational study using penile traction for men with curvature <50° demonstrated increased penile length (1.4 cm on average) and decreased curvature over 1 year of treatment [83]. A second, recently published prospective, uncontrolled study of 11 men, combined intralesional verapamil with penile traction, applied, on average for 3.6 h/day, demonstrated subjective and objective decreases in penile curvature [84]. While the small size of this study and the absence of a control group limit the conclusions one can draw from it, this pilot study supports the feasibility of this approach. One of the primary concerns of men with PD is the frequent loss of penile length [23]. These mechanical devices may offer patients an effective way to minimize this feared and psychologically devastating symptom. Larger, controlled studies are necessary to verify these results; however, this therapy presents a novel approach to the treatment of PD that may be beneficial for many individuals.

Shock Wave Therapy

Several groups have utilized shock wave therapy successfully to treat penile plaques and curvature [85–87]. Local and/or regional anesthesia is needed occasionally for the procedure and while minor skin hematomas were very common (76 %), both this adverse event and mild urethral bleeding (8 %) resolved spontaneously. The only placebo-controlled trial for shock wave therapy demonstrated a significant reduction in penile pain; however, they did illustrate worsening curvature in the shock wave group [88].

Conclusion

Peyronie's disease is an acquired disorder of penis resulting from inflammation. This largely results in physical changes which include penile curvature and plaque formation, functional changes including erectile dysfunction, as well as significant psychological symptoms. Careful physical and psychosexual examination is necessary to properly identify the stage and extent of the disease. The use of adjunct diagnostic tools including B-mode ultrasound imaging as well as color duplex imaging significantly aids in the ability to better offer prognostic information to the patient and direct different treatment options. Multiple medical therapies exist with variable response rates, and currently there is only one FDA approved treatment.

References

1. Musitelli S, Bossi M, Jallous H. A brief historical survey of "Peyronie's disease". J Sex Med. 2008; 5(7):1737–46.
2. Lindsay MB, Schain DM, Grambsch P, Benson RC, Beard CM, Kurland LT. The incidence of Peyronie's disease in Rochester, Minnesota, 1950 through 1984. J Urol. 1991;146:1007–9.

3. Smith B. Subclinical Peyronie's disease. Am J Clin Pathol. 1969;52:385–90.
4. Sommer F. Epidemiology of Peyronie's disease. Int J Impot Res. 2002;14:379–83.
5. Rhoden E. Prevalence of Peyronie's disease in men over 50-y-old from Southern Brazil. Int J Impot Res. 2001;13:291–3.
6. Mulhall J. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol. 2004;171:2350–3.
7. Shiraishi K, Shimabukuro T, Matsuyama H. The prevalence of Peyronie's disease in Japan: a study in men undergoing maintenance hemodialysis and routine health checks. J Sex Med. 2012;9(10):2716–23.
8. Lue T. The anatomy of the tunica albuginea in the normal penis and Peyronie's disease. J Urol. 1997; 157:276–81.
9. Smith JF, Brant WO, Fradet V, Shindel AW, Vittinghoff E, Chi T, et al. Penile sonographic and clinical characteristics in men with Peyronie's disease. J Sex Med. 2009;6(10):2858–67.
10. Gonzalez-Cadavid NF. Mechanisms of penile fibrosis. J Sex Med. 2009;6 Suppl 3:353–62.
11. Sommers KD. Fibrin deposition in Peyronie's disease plaque. J Sex Med. 1997;157:311–5.
12. Lue T. Peyronie's disease—an anatomically-based hypothesis and beyond. Int J Impot Res. 2002; 14:411–3.
13. Rhoden EL, Riedner CE, Fuchs SC, Ribeiro EP, Halmenschlager G. A cross-sectional study for the analysis of clinical, sexual and laboratory conditions associated to Peyronie's disease. J Sex Med. 2010;7(4 Pt 1):1529–37.
14. Deveci S, Hopps CV, O'Brien K, Parker M, Guhring P, Mulhall JP. Defining the clinical characteristics of Peyronie's disease in young men. J Sex Med. 2007;4(2):485–90.
15. Capogrosso P, Colicchia M, Ventimiglia E, Castagna G, Clementi MC, Suardi N, et al. One patient out of four with newly diagnosed erectile dysfunction is a young man—worrisome picture from the everyday clinical practice. J Sex Med. 2013;10(7):1833–41.
16. El-Sakka AI, Tayeb KA. Peyronie's disease in diabetic patients being screened for erectile dysfunction. J Urol. 2005;174(3):1026–30.
17. Tal R, Heck M, Teloken P, Siegrist T, Nelson CJ, Mulhall JP. Peyronie's disease following radical prostatectomy: incidence and predictors. J Sex Med. 2010;7(3):1254–61.
18. Brant WO, Bella AJ, Garcia MM, Tantiwongse K, Dean RC, Lue TF. Isolated septal fibrosis or hematoma—atypical Peyronie's disease? J Urol. 2007;177(1):179–82. discussion 83.
19. Kadioglu A, Sanli O, Akman T, Canguven O, Aydin M, Akbulut F, et al. Factors affecting the degree of penile deformity in Peyronie disease: an analysis of 1001 patients. J Androl. 2011;32(5):502–8.
20. Kadioglu A, Tefekli A, Erol B, Oktar T, Tunc M, Tellaloglu S. A retrospective review of 307 men with Peyronie's disease. J Urol. 2002;168(3):1075–9.
21. Kadioglu A, Tefekli A, Cayan S, Kandirali E. Color Doppler ultrasound assessment of penile vascular system in men with Peyronie's disease. Int J Impot Res. 2000;12:263–7.
22. Nelson CJ, Diblasio C, Kendirci M, Hellstrom W, Guhring P, Mulhall JP. The chronology of depression and distress in men with Peyronie's disease. J Sex Med. 2008;5(8):1985–90.
23. Smith JF, Walsh TJ, Conti SL, Turek P, Lue T. Risk factors for emotional and relationship problems in Peyronie's disease. J Sex Med. 2008;5(9):2179–84.
24. Hellstrom WJ, Feldman R, Rosen RC, Smith T, Kaufman G, Tursi J. Bother and distress associated with Peyronie's disease: validation of the Peyronie's disease questionnaire. J Urol. 2013;190(2):627–34.
25. Coyne KS, Currie BM, Thompson CL, Smith TM. Responsiveness of the Peyronie's disease questionnaire (PDQ). J Sex Med. 2015;12(4): 1072–9.
26. Bacal V, Rumohr J, Sturm R, Lipshultz LI, Schumacher M, Grober ED. Correlation of degree of penile curvature between patient estimates and objective measures among men with Peyronie's disease. J Sex Med. 2009;6(3):862–5.
27. Hakim L. Peyronie's disease: an update—the role of diagnostics. Int J Impot Res. 2002;14:321–3.
28. Pryor J. Clinical presentations of Peyronie's disease. Int J Impot Res. 2002;14:414–7.
29. Andresen R. Imaging modalities in Peyronie's disease. An interpersonal comparison of ultrasound sonography, X-ray mammography technique, computerized tomography, and nuclear magnetic resonance in 20 patients. Eur Urol. 1998;34:128–34.
30. Hauck E. Diagnostic value of magnetic resonance imaging in Peyronie's disease—a comparison both with palpation and ultrasound in the evaluation of plaque formation. Eur Urol. 2003;43(3):293–300.
31. Bertolotto M. Painful penile induration: imaging findings and management. Radiographics. 2009;29: 477–93.
32. Bekos A, Arvaniti M, Hatzimouratidis K, Moysidis K, Tzortzis V, Hatzichristou D. The natural history of Peyronie's disease: an ultrasonography-based study. Eur Urol. 2008;53(3):644–50.
33. Breyer BN, Shindel AW, Huang YC, Eisenberg ML, Weiss DA, Lue TF, et al. Are sonographic characteristics associated with progression to surgery in men with Peyronie's disease? J Urol. 2010;183(4): 1484–8.
34. Trost LW, Gur S, Hellstrom WJ. Pharmacological management of Peyronie's disease. Drugs. 2007; 67:527–45.
35. Azzi A. Molecular mechanism of alpha-tocopherol action. Free Radic Biol Med. 2007;43(1):16–21.
36. Inal T, Tokatli Z, Akand M, Ozdiler E, Yaman O. Effect of intralesional interferon-alpha 2b combined with oral vitamin E for treatment of early stage Peyronie's disease: a randomized and prospective study. Urology. 2006;67(5):1038–42.
37. Safarinejad MR, Hosseini SY, Kolahi AA. Comparison of vitamin E and propionyl-l-carnitine, separately or in

combination, in patients with early chronic Peyronie's disease: a double-blind, placebo controlled, randomized study. J Urol. 2007;178:1398–403.
38. Prieto Castro RM, Leva Vallejo ME, Regueiro Lopez JC, Anglada Curado FJ, Alvarez Kindelan J, Requena Tapia MJ. Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. BJU Int. 2003;91:522–4.
39. Brigelius-Flohe R. Adverse effects of vitamin E by induction of drug metabolism. Genes Nutr. 2007; 2(3):249–56.
40. Bremer J. Carntine—metabolism and functions. Physiol Rev. 1983;63(4):1421–80.
41. Cavallini G, Biagiotti G, Koverech A, Vitali G. Oral propionyl-l-carnitine and intraplaque verapamil in the therapy of advanced and resistant Peyronie's disease. BJU Int. 2002;89:895–900.
42. Biagiotti G, Cavallini G. Acetyl-L-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. BJU Int. 2001;88:63–7.
43. Karlic H, Lohninger A. Supplementation of L-carnitine in athletes: does it make sense? Nutrition. 2004;20(7–8):709–15.
44. Wagenknecht LV. Differential therapies in various stages of penile induration. Arch Esp Urol. 1996;49(3):285–92.
45. Carson CC. Potassium para-aminobenzoate for the treatment of Peyronie's disease: is it effective? Tech Urol. 1997;3(3):135–9.
46. Weidner W, Ekkehard WH, Schnitker J. Potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective. Placebo-controlled randomized study. Eur Urol. 2005;47:530–6.
47. McCarty MF. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline. Med Hypotheses. 1999;52(5):465–77.
48. Delanian S, Porcher R, Balba-Mekias S, Lefair J. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol. 2003;21(13):2545–50.
49. Tittelbach J, Graefe T, Wollina U. Painful ulcers in calciphylaxis—combined treatment with maggot therapy and oral pentoxifylline. J Dermatolog Treat. 2001;12(4):211–4.
50. Aygenc E, Celikkanat S, MKaymakci M, Aksaray F, Ozdem C. Prophylactic effect of pentoxifylline on radiotherapy complications: a clinical study. Head Neck Surg. 2004;130(3):351–6.
51. Boldt J, Brosch C, Piper SN, Suttner S, Lehmann A, Werline C. Influence of prophylactic use of pentoxifylline on postoperative organ function in elderly cardiac surgery patients. Crit Care Med. 2001; 29(5):952–8.
52. Noel C, Copin M, Hazzan M, Labalette M, Susen S, Lelievre G, et al. Immunomodulatory effect of pentoxifylline during human allograft rejection: involvement of tumor necrosis factor-[alpha] and adhesion molecules. Transplantation. 2000;69(6):1102–7.
53. Valente E, Vernet D, Ferrini M, Qian A, Rajfer J, Gonzalez-Cadavid F. L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and related fibroblast cultures. Nitric Oxide. 2003;9:229–44.
54. Takami M, Cho ES, Lee SY, Kamijo R, Yim M. Phosphodiesterase inhibitors stimulate osteoclast formation via TRANCE/RANKL expression in osteoblasts: possible involvement of ERK and p38 MAPK pathways. FEBS Lett. 2005;579:832–8.
55. Rajfer J, Gore J, Kaugman J, Gonzalez-Cadavid NF. Case report: Avoidance of palpable corporal fibrosis due to priapism with upregulators of nitric oxide. J Sex Med. 2005;3:173–6.
56. Brant WO, Dean RC, Lue TF. Treatment of Peyronie's disease with oral pentoxifylline. Nat Clin Pract Urol. 2006;3(2):111–5.
57. Colletta AA, Wakefield LM, Howell F, Roozendaal KOE, Danielpour D, Ebbs SR, et al. Anti-oestrogens induce that secretion of active transformation growth factor beta from human fetal fibroblasts. Br J Cancer. 1990;62:405–6.
58. Hauck EW, Diemer T, Schmelz HU, Weidner W. A critical analysis of nonsurgical treatment of Peyronie's disease. Eur Urol. 2006;49(6):987–97.
59. Diegelmann R, Peterkofsky B. Inhibition of collagen secretion from bone and cultured fibroblasts by microtubular disruptive drugs. Proc Natl Acad Sci U S A. 1972;69(4):892–6.
60. Safarinejad MR. Therapeutic effects of colchicine in the management of Peyronie's disease: a randomized double-blind, placebo-controlled study. Int J Impot Res. 2004;16(3):238–43.
61. Gonzalez-Cadavid NF, Rajfer J. Treatment of Peyronie's disease with PDE5 inhibitors: an antifibrotic strategy. Nat Rev Urol. 2010;7(4):215–21.
62. Montorsi R, Corbin J, Phillips S. Review of phosphodiesterases in the urogenital system: new directions for therapeutic intervention. J Sex Med. 2004;1: 322–36.
63. Chung E, Deyoung L, Brock GB. The role of PDE5 inhibitors in penile septal scar remodeling: assessment of clinical and radiological outcomes. J Sex Med. 2011;8(5):1472–7.
64. Lee RC, Ping JA. Calcium antagonists retard extracellular matrix production in connective tissue equivalent. J Surg Res. 1990;49(5):463–6.
65. Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. Urology. 1998;51(4): 620–6.
66. Cavallini G, Modenini F, Vitali G. Open preliminary randomized prospective clinical trial of efficacy and safety of three different verapamil dilutions for intraplaque therapy of Peyronie's disease. Urology. 2007;69(5):950–4.
67. Russell S, Steers W, McVary KT. Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. Eur Urol. 2007;51(3):640–7.
68. Duncan MR, Hasan A, Berman B. Pentoxifylline, pentifylline, and interferons decrease type I and III

procollagen mRNA levels in dermal fibroblasts: evidence for mediation by nuclear factor 1 down-regulation. J Invest Dermatol. 1995;104(2):282–6.
69. Duncan MR, Berman B, Nseyo UO. Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by interferons-alpha, -beta and -gamma. Scand J Urol Nephrol. 1991;25(2):89–94.
70. Hellstrom WJG, Kendirci M, Matern R, Cockerham Y, Myers L, Sikka SC, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon α-2b for minimally invasive treatment for Peyronie's disease. J Urol. 2006;176(1):394–8.
71. Gelbard M, Walsh R, Kaufman JJ. Clostridial collagenase and Peyronie disease. Urology. 1980;15(5):536.
72. Gelbard MK, Walsh R, Kaufman G. Collagenase for Peyronie's disease experimental studies. Urol Res. 1982;10(3):135–40.
73. Gelbard MK, Lindner A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. J Urol. 1985;134(2):280–3.
74. Gelbard M, Goldstein I, Hellstrom WJ, McMahon CG, Smith T, Tursi J, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. J Urol. 2013;190(1):199–207.
75. Bartsch G, Menander-Huber KB, Huber W, Marberger H. Orgotein, a new drug for the treatment of Peyronie's disease. Eur J Rheumatol Inflamm. 1981;4(2):250–9.
76. Gustafson H, Johansson B, Edsmyr F. Peyronie's disease: experience of local treatment with Orgotein. Eur Urol. 1981;7(6):dd346–8.
77. Francesco M, Salonia A, Guazzoni G, Barbeiri L, Colombo R, Brausi M, et al. Transdermal electromotive multi-drug administration for Peyronie's disease: preliminary results. J Androl. 2000;21:85–90.
78. Riedl CR, Sternig P, Galle G, Langmann F, Vcelar B, Vorauer K, et al. Liposomal recombinant human superoxide dismutase for the treatment of Peyronie's disease: a randomized placebo-controlled double-blind prospective clinical study. Eur Urol. 2005; 48(4):656–61.
79. Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Giurioli A, Jannini EA, et al. A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. J Urol. 2004;171(4):1605–8.
80. Greenfield JM, Shah SJ, Levine LA. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. J Urol. 2007;177(8):972–5.
81. Fitch III WP, Easterling WJ, Talbert RL, Bordovsky MJ, Mosier M. Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's disease—a placebo-controlled pilot study. J Sex Med. 2007;4(2):477–84.
82. Martin DJ, Badwan K, Parker M, Mulhall JP. Transdermal application of verapamil gel to the penile shaft fails to infiltrate the tunica albuginea. J Urol. 2002;168(6):2483–5.
83. Gontero P, Di Marco M, Giubilei G, Bartoletti R, Pappagallo G, Tizzani A, et al. Use of penile extender device in the treatment of penile curvature as a result of Peyronie's disease. Results of a phase II prospective study. J Sex Med. 2009;6(2):558–66.
84. Levine LA, Newell M, Taylor FL. Penile traction therapy for treatment of Peyronie's disease: a single-center pilot study. J Sex Med. 2008;5(6):1468–73.
85. Claro J, Passerotti C, Figueiredo Neto A, Nardozza A, Ortiz V, Srougi M. An alternative non-invasive treatment for Peyronie's disease. Int Braz J Urol. 2004;30(3):199–204.
86. Abdel-Salam Y, Budair Z, Renner C, Frede T, Rassweiler J, El-Annany F, et al. Treatment of Peyronie's disease by extracorporeal shockwave therapy: evaluation of our preliminary results. J Endourol. 1999;13(8):549–52.
87. Skolarikos A, Alargof E, Rigas A, Deliveliotis C, Konstantinidis E. Shockwave therapy as first-line treatment for Peyronie's disease: a prospective study. J Endourol. 2005;19(1):11–4.
88. Hatzichristodoulou G, Meisner C, Gschwend JE, Stenzl A, Lahme S. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. J Sex Med. 2013;10(11):2815–21.

Injection Therapy for Peyronie's Disease

22

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Introduction

Peyronie's disease (PD) is a sensitive topic for many patients and the medical community still lacks basic knowledge about this condition. PD is not a rare condition, as it has been reported that anywhere from 3.2 to 8.9 % of adult men have PD [1–3]. Similarly, it is not a novel condition, as it was named after the French surgeon Francois Gigot de LaPeyronie (LaPeyronie, fittingly, translates to "the little stone"), who lived in the 17th and 18th centuries and described PD in a treatise on ejaculatory failure [4]. For these reasons, PD has not received the medical attention it fully deserves.

PD is categorized into an early or acute phase, characterized by pain and progressive deformity, and a stable or chronic phase, characterized by diminished pain, organization of a plaque, and penile deformity with erection [5]. Any surgical correction should be postponed until there is stabilization of the deformity so that multiple interventions are not needed; theoretically, non-surgical treatment in the acute phase (e.g., with oral agents, traction therapy and intralesional injections) may prevent plaque organization and lessen eventual erectile deformity [6]. This chapter discusses intralesional injection therapy (ILI), which is one of many modalities in the treatment of PD. Focus is placed on the mechanism of action of the different pharmacologic agents described, the history of their use, specific indications or contraindications if applicable, common injection regimens, the most frequent and serious side effects, and the efficacy of particular treatments (Table 22.1).

Corticosteroids

While the exact pathophysiology of PD is yet to be elucidated, one proposed mechanism is that an inciting event (trauma or microtrauma to the penis, e.g., during sexual intercourse) causes local inflammation within the tunica albuginea, which in genetically susceptible men leads to abnormal wound healing characterized by fibrous plaque formation, and the physical manifestation of the disease [7, 8]. Corticosteroids were the first known ILI agent employed in the treatment of PD, with documented use as early as 1952 by Teasley [9]. Their use is rational when one

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Table 22.1 Selected large single-agent intralesional injection therapy studies for Peyronie's disease

Authors	Year	Design	Therapy	*N*	Duration	Findings
Levine et al.	2002	Nonrandomized prospective	Verapamil 10 mg in 10 cc normal saline, ILI q 2 weeks × 12 injections	156	6 months	140 patients completed study. 62 % of patients with decrease in penile curvature (mean 31°, range 5–90), 8 % increase in penile curvature (mean 20°, range 20–45), and 30 % with no change in curvature.
Hellstrom et al.	2006	Randomized single blind, placebo controlled	Interferon a-2B 5 MU ILI q 2 weeks × 12 injections	117	3 months	Statistically significant improvement in patient's penile curvature (27 % mean curvature improvement in treatment arm vs. 9 % in placebo), plaque size (mean decrease of 55 % in treatment arm vs. 20 % in placebo), and pain with erections (68 % resolution of pain in treatment arm vs. 28 % in placebo) with interferon a-2B treatment. No statistically significant improvement in IIEF score (mean increase of 13 % in treatment arm vs. 6 % in placebo).
Gelbard et al.	2013	Randomized double blind, placebo controlled	Collagenase clostridium histolytiucm 0.58 mg ILI q24–72 h × 2 injections, every 6 weeks (maximum 8 injections total)	832	52 weeks	Statistically significant improvement in penile curvature in the treatment group (mean 34 %, corresponding to a $-17.0 \pm 14.8°$) as compared to control group (mean 18 % improvement in curvature, corresponding to a $-9.3 \pm 13.6°$ ($p < 0.001$)). Statistically significant improvement in the PD symptom bother domain score (treatment group mean improvement PD bother score is -2.8 ± 3.8 points), superior (statistically significant, $p = 0.0037$) to the control group (mean improvement -1.8 ± 3.5 points).

ILI intralesional injection therapy, *IIEF* International Index of Erectile Function, *PD* Peyronie's disease

considers steroids' long-known anti-inflammatory properties and their ability to suppress collagen formation [10]. In 1954, Teasley published a retrospective study of 24 patients that were treated with corticosteroids administered by ILI with promising results [11]. A number of subsequent studies, by Bodner in 1954 [12], Furey in 1957 [9], Desanctis in 1967 [13], Toksu in 1971 [14], Winter in 1975 [15], and Williams in 1980 [16], all described the use of corticosteroid by ILI in the treatment of PD. While these studies showed varying levels of improvement, these studies were small, nonrandomized, and, in general, of poor level of evidence [6]. Presently, ILI of corticosteroids is not recommended due to its unproven efficacy in treatment, and because it

causes local atrophy of tissue planes within the penis that makes subsequent surgical intervention more difficult [10].

Verapamil

After corticosteroids, the next pharmacologic agent utilized for ILI therapy of PD was the calcium channel blocker (CCB) verapamil. Fibrous PD plaques are composed of extracellular matrix (ECM) macromolecules such as collagen, glycosaminoglycans (GAGs), and fibronectin [17]. CCBs like verapamil have been shown to inhibit the secretion of these molecules, forming the theoretical basis of their use in treating PD [17]. They also have been hypothesized to increase the proteolytic activity of collagenase, the enzyme responsible for breaking down the collagen that characterizes PD plaques [18].

Verapamil was first used in 1994 on 14 patients in a dose-escalating study, starting with 1 mmol solution injected biweekly into the plaque via 100–150 plaque punctures with a 25 gauge needle (multi injection technique). The concentration of the drug was then doubled every month until a 10-milligram (mg) dose was achieved. The authors of the study noted subjective improvement in pain, penile curvature, and sexual performance in 91 %, 42 %, and 58 % of patients, respectively. Furthermore, the authors concluded that ILI of verapamil was safe, with no serious adverse events, with the only noted side effect being temporary ecchymosis at the injection site [17].

Subsequent studies of verapamil ILI were able to reproduce these early promising findings. In 1997, Levine published a follow-up study of 46 men with PD who were treated with 10 mg verapamil diluted to 10 cubic centimeters (cc) every other week for a total of 12 injections over 24 weeks. Importantly, this study not only demonstrated an objective improvement in curvature in 54 % of patients, but also an improvement in the ability to engage in coitus in 72 % of patients [19].

The first randomized placebo-controlled trial with ILI of verapamil took place in 1998 when Rehman et al. treated 14 men with either weekly injections of 10–27 mg verapamil ILI, or with a saline solution placebo [20]. At the end of 6 months the authors noted a statistically significant improvement in plaque volume, and a trend towards improvement in penile curvature, in the verapamil group as compared to placebo [20].

Levine et al. then published an uncontrolled study of 156 men with PD (140 of whom completed the therapy), treated again with injections of 10 mg verapamil in 10 cc saline solution injected every other week for 24 weeks. Again, a little over half of all patients who completed therapy had objective decrease in penile curvature [21].

Subsequent trials with verapamil ILI therapy, however, were less conclusive in their results. In 2007, Bennett et al. published an uncontrolled study of 94 patients with predominantly dorsal plaques who were treated with a course of six verapamil ILIs. They found that only 18 % of study subjects experienced improvement in their penile deformity, while 60 % had unchanged curvature, and 22 % experienced worsening of penile curvature. The only finding that proved statistically significant in the study was an improvement in penile rigidity adequate for intercourse [22]. The authors concluded verapamil injections were beneficial in stabilizing lesions, but that patients' expectations regarding treatment benefits need to be tempered.

In 2007, Cavallini et al. published a study of 77 patients randomized to receive different dilutions of verapamil ILI, concluding that the most dilute (and greatest volume) of verapamil solution (10 mg diluted in 20 cc solution) was more efficacious than the 10 mg given in 10 or 4 cc of solution. The study noted a statistically significant decrease in plaque area in all three groups, and a statistically significant improvement in penile curvature in the patients receiving the greatest volume of verapamil (i.e., the most dilute concentration of verapamil), though not in the other two groups receiving smaller volumes of less concentrated drugs [23].

In 2009, Shirazi et al. published a randomized controlled trial of 80 men with PD who were

treated in the same fashion as in Levine's original studies (10 mg verapamil in 10 cc normal saline (NS), given every other week for 24 weeks) and found no significant difference between the verapamil and NS control groups with regard to penile curvature, plaque size, or erectile dysfunction [24].

In 2010, Soh et al. published the first study looking at the ILI of a CCB other than verapamil in the treatment of PD. Specifically, the study utilized nicardipine, a dihydropyridine (DHP) CCB that, in vitro, was more effective than non-DHP CCB (e.g., verapamil) in reducing extracellular matrix production. The study was single-blind, placebo-controlled, and treated 37 men with PD to ILI of 10 mg of nicardapine dissolved in 10 cc of NS every other week for 12 weeks, and 37 men to ILI of 10 cc of NS in the same fashion. The authors found statistically significant improvement in pain score, International Index of Erectile Function (IIEF) score and decrease in plaque size at 48 weeks in the treatment arm versus placebo, but no significant difference in improvement in penile curvature between the two groups [25].

In 2011, Moskovic et al. published an uncontrolled study of 131 patients who received six injections of 10 mg of verapamil in 5 cc solution, examining baseline characteristics that could be used to predict efficacy of ILI therapy. The authors concluded that younger age and larger baseline curvature were significantly correlated with improvement in curvature with therapy [26].

While the above trials have treated men with PD with dorsal plaques, in 2015 Berookhim et al. described their institution's use of ILI of verapamil on 154 men with PD, of which 10 were treated with ventral plaques. They reported a similar efficacy of therapy in the patients treated with ventral plaques as those with dorsal plaques, with 40% of patients with ventral plaques reporting at least 10° improvement in curvature, 50% reporting stable curvature, and 10% reporting worsening of curvature. The authors conclude that verapamil ILI is safe to use for ventral plaques, so long as special attention is given to avoiding midline injections into the urethra [27].

Interferon

In 1991, Duncan et al. published a report on the effect of human recombinant interferons (IFNs) on cells cultured from PD plaques. The authors stated that these cells resembled myofibroblasts observed in wound healing and were responsible for collagen deposition and other ECM components including GAGs. They further hypothesize how these cells cultured from PD plaques are similar to fibroblasts seen in scleroderma and keloid lesions that are also postulated to cause excessive deposition of ECM components [28].

While Duncan et al. provided the theoretical basis for the use of IFN in the treatment of PD, in 1995 Wegner et al. was the first to perform ILI with IFN [29]. A total of 25 patients were treated with interferon a-2B (IFN a-2B), 1 million units (MU) given weekly for 5 weeks. The authors demonstrated improvement in plaque size in 7 patients, stability of plaque size in 12 patients, and increase in plaque size in 6 patients. They concluded the drug was safe, with the most common side effects being myalgia and fever seen in 4 of the 25 patients. They also noted that the treatment appeared to be more efficacious in early plaque lesions and in patients without evidence of calcifications, and suggested that further dosing studies were needed [29].

In 1997, Wegner published a new series involving 30 additional men with early PD treated with ILI INF a-2B 3 MU weekly for 3 weeks, and concluded that their regimen was not an effective treatment, since approximately 25% of men had progression of the disease with IFN therapy, and an intolerable side effect profile that caused fevers greater than 38 °C after 74 of the 90 total injections [30].

That same year, however, Judge et al. published a series of 13 men treated with either INF a-2B 1.5 MU, three times weekly for 3 weeks (10 of 13 patients), or treated with same regimen of NS ILI (3 of 13 patients). The authors found 6 of the 10 patients treated with IFN had reduction in their pain with erections and had improvement in their degree of curvature (mean improvement 20°), while none of the patients treated with NS had improvement in these respective categories.

They also noted the most common side effect in the treatment group was a transient flu-like illness, though stated it lessened with each subsequent injection, and was often controlled by taking 1 g of oral paracetamol after receiving the injection [31].

Subsequent small-scale studies continued to produce more promising results. A study by Ahuja et al. in 1999 reported on 21 patients treated with IFN a-2B 1 MU biweekly for 6 months, and found statistically significant reduction in pain, penile curvature, and plaque size in treated patients [32]. Another study by Dang et al. in 2004 looked at 21 patients treated with injections of IFN a-2B 2 MU twice weekly for 6 weeks. Of these 21 patients, 7 patients received a 6-week course of NS ILI twice weekly prior to starting IFN a-2B ILI therapy. The authors found significant improvements in penile pain and curvature in the majority of patients after treatment with IFN a-2B ILI therapy. They also noted that subjective improvements in pain and erectile curvature were not seen in the saline control group prior to beginning IFN therapy [33].

In 2005, Kendirci et al. published the first randomized, placebo-controlled trial with intralesional IFN on 39 patients, of which 19 were treated with IFN a-2B 5 MU every other week for six injections, and 20 patients with 10 cc NS ILI every other week for six injections. The study is notable not only for the increased dose of IFN a-2B that subjects received (5 MU per injection as compared to 3 MU or less in previous studies), but also in that it examined the effect that IFN a-2B ILI therapy had on penile hemodynamic parameters. The authors observed that, in addition to improving penile curvature, decreasing plaque size, and decreasing pain with erections, IFN a-2B ILI therapy also improved penile hemodynamics (31.5 % of patients with nonvascular penile blood flow prior to ILI therapy versus 57.8 % after treatment). This improvement in penile blood flow did not, however, correspond with a significant improvement in erectile function in the treatment group [34].

In 2006, the largest IFN a-2B study to date was published. Hellstrom et al. performed a single-blind, placebo-controlled, randomized study of IFN a-2B ILI, with 55 patients receiving IFN a-2B ILI 5 MU in 10 cc NS every other week for 12 weeks, versus 62 patients randomized to receive the same dosing of NS ILI control. Not only was this trial notable for its size, but also for its comprehensiveness. Patients were evaluated for pre- and post-intervention penile curvature, plaque size, pain with erections, as well as erective function, as measured by the patient's IIEF score. Again, there was statistically significant improvement in patient's penile curvature (27.01 % mean curvature improvement in treatment arm versus 8.87 % in placebo), plaque size (mean decrease of 54.6 % in treatment arm versus 19.8 % in placebo), and pain with erections (67.7 % resolution of pain in treatment arm versus 28.1 % in placebo) with IFN a-2B treatment. The study did not find a statistically significant improvement in IIEF score after 12 weeks of injections (mean increase of 13.53 % in treatment arm versus 5.96 % in placebo). Hellstrom et al. concluded IFN a-2B was an effective minimally invasive, and generally well-tolerated, intervention in the treatment of PD [35].

More recently, Trost et al. published a series reviewing 127 patients treated with IFN a-2B ILI from 2001 to 2012 at a single institution. Patients were treated with IFN a-2B 2 MU biweekly for a median number of 12 injections. Again, erectile function and penile hemodynamics were studied before and after receiving IFN a-2B ILI therapy. Of the 127 patients, 54 % responded to therapy with an average improvement in erectile curvature of 9°, while 10.2 % of patients had progression of their disease while on IFN therapy, and 18.9 % of patients had stability of their disease. The trial was significant in that it showed equivalent outcomes regardless of when therapy was initiated (acute setting versus chronic), and in that it showed no improvement in patients treated with two courses of IFN a-2B ILI injections as opposed to one course of 12 injections with IFN a-2B. In addition, the trial reproduced the results from previous trials showing that IFN a-2B ILI improved penile hemodynamics without a corresponding improvement in erectile function [36]. It is also worth noting that at our institution, IFN a-2B ILI has been safely used on patients with ventral PD plaques with rates of efficacy similar as to patients treated with dorsal PD plaques.

Collagenase

Although ILI of collagenase clostridium histolyticum (CCH) was only FDA approved for the treatment of PD in 2013, its potential role in the treatment of PD was first examined almost 30 years prior. In 1982, Gelbard et al. published in vitro studies of CCH applied to tunica albuginea and PD plaque tissue samples. The authors concluded that CCH was effective in the dissolution of both normal tunica albuginea and the intended PD plaques. However, they went on to state that there was very limited dispersion of the enzyme from its applied site, and that elastic tissues were preserved. Most importantly, CCH did not digest vascular smooth muscle cells, a property that protects all penile vasculature with the exception of the small venules. This same property also prevents nerve axons from being degraded, as their myelin sheaths are comprised of lipids not digested by CCH [37].

First used in the treatment of PD in 1980s, CCH was not pursued again in the treatment of PD until quite recently. In 1985, Gelbard et al. published a report of 31 patients treated with 420–920 U of purified CCH enzyme given in 1 cc solution. As this was the first time CCH was used in the treatment of PD, its immunologic affects were unknown and the researchers decided to administer the drug on 3 consecutive days in order to limit the risk of a theoretical hypersensitivity reaction. Gelbard et al. concluded that 65 % of the patients had objective improvement in the deformity of their disease, and pain with erection was eliminated in 93 % of patients. They also noted that the injections appeared safe for use without systemic side effects, with the most serious side effect being a small corporeal wall rupture at the site of injection that occurred in one patient [38].

The first randomized, double-blind, placebo-controlled trial using intralesional CCH was published in 1993 by Gelbard et al. Subjects were injected with a one-time dose of 6000–14,000 U of CCH depending on the severity of their erection deformity, and were followed for 3 months to assess treatment response. The researchers discovered the injections to be safe, but only able to improve penile curvature by approximately 20°, and thus concluded CCH to be most effective for patients with less severe curvatures [39].

In 1998, Jordan published a study of 25 men with PD treated with three injections of 10,000 U of collagenase given over 7–10 days, and repeated with three additional ILI at 3 months. The authors found statistically significant improvement in penile deformity (mean improvement of 12.7° at 3 months), and again noted the injection to be generally well tolerated, with the most common adverse events being penile pain, edema and ecchymosis at the site of injection [40].

In 2010, intralesional CCH was approved for the treatment of Dupuytren's contracture in patients with a palpable cord, and there was renewed interest in using CCH in the treatment of PD [41]. As such, in September 2010 a number of centers in the USA began accruing patients for two large, identical, phase 3 studies (randomized, double-blind, placebo-controlled) named IMPRESS I and II (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) with 417 and 415 patients enrolled, respectively. The treatment arm of the studies involved a maximum of four treatment cycles of CCH ILI 0.58 mg, each cycle consisting of two ILI given 24–72 h apart, followed by penile plaque modeling 24–72 h after the last injection. Therapy was discontinued if the penile curvature was decreased to less than 15°, or if the investigator deemed further treatment to be not clinically indicated. Exclusion criteria in IMPRESS I and II were patients with calcified plaques and/or ventral lesions. In addition, patients were required to have at least a 30° curvature with erections to be eligible for the trial [42].

The study reported a mean improvement in penile curvature in the treatment group of 34 %, corresponding to a $-17.0 \pm 14.8°$. This was found to be significantly superior to the control group, who on average saw an 18.2 % improvement in curvature, corresponding to a $-9.3 \pm 13.6°$ ($p < 0.001$). In addition, the researchers observed a statistically significant improvement in the PD symptom bother domain score, which is comprised of four questions and whose total score can range from 0 to 16. In the treatment group the average PD bother score improvement was

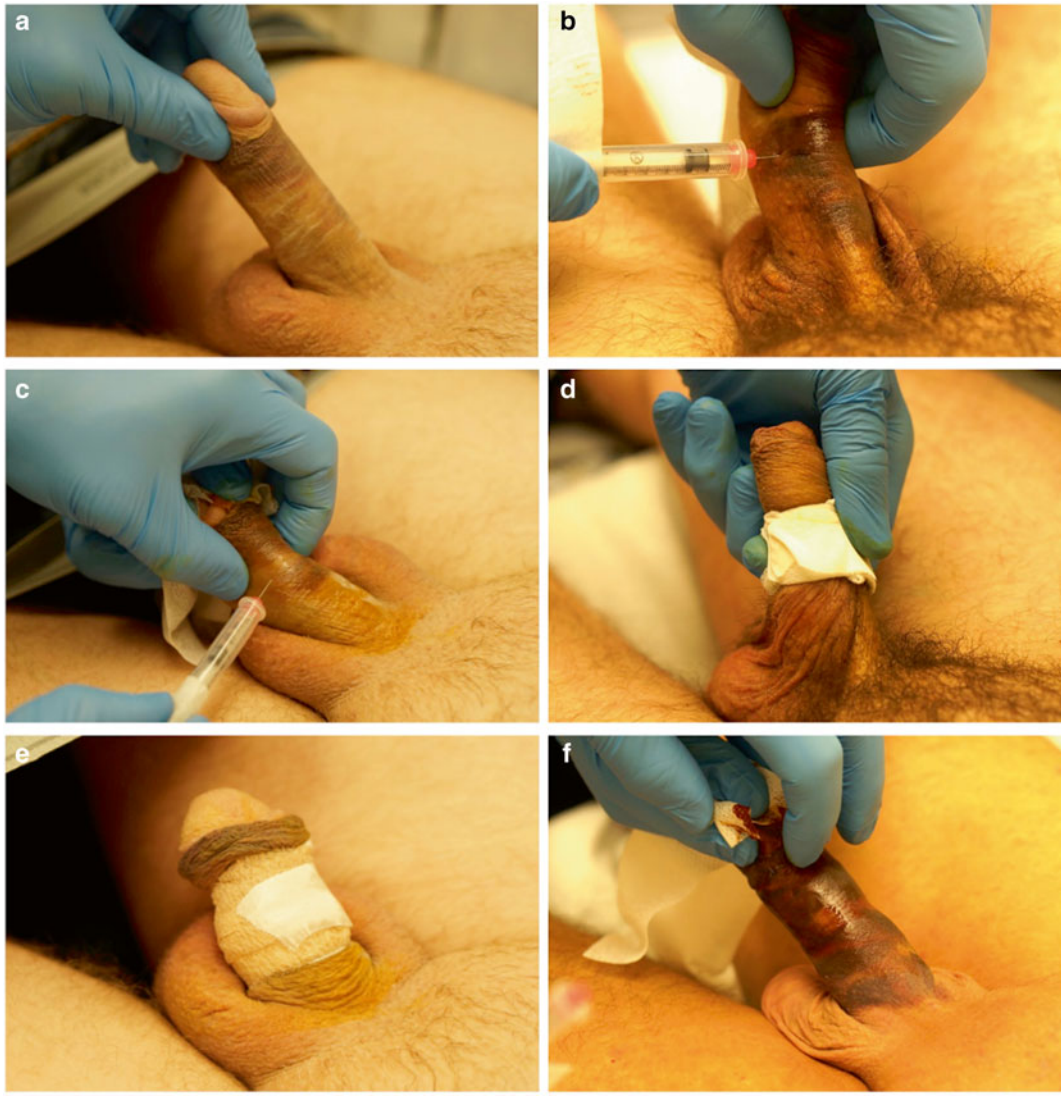

Fig. 22.1 (**a**–**f**) Intralesional injection of collagenase clostridium histolyticum for Peyronie's disease. (**a**) Penis is held in straight position and prepped in a sterile manner. (**b** and **c**) Using a 27-gauge 1⁄2-in. needle, 0.58 mg CCH (0.25 ml) is injected into the Peyronie's plaque in alignment with the point of maximal concavity. The needle should not go beneath the plaque or perpendicularly towards the corpora cavernosa. (**d**) Following injection, the penis is first wrapped with sterile gauze. (**e**) Then wrapped with a Coban dressing. (**f**) Example of a penile hematoma that can occur after injection

−2.8 ± 3.8 points, which was superior (statistically significant, $p = 0.0037$) to the control group that changed −1.8 ± 3.5 points [42].

As a result of the study, on December 6, 2013 the FDA approved collagenase for the treatment of PD with the above indications and contraindications [43]. Figure 22.1a–f shows photos of ILI of CCH for PD.

Penile Traction Therapy with ILI

While this chapter focuses on intralesional therapies in the treatment of PD, there are a number of trials that use combination of intralesional, oral, and penile traction therapies (PTT), among other treatment modalities. This section aims to focus

on PTT, which has been used in combination with a number of ILI studies.

In 2008, Abern and Levine published a pilot study looking at verapamil ILI with and without concurrent PTT. They described treating 44 patients with verapamil ILI alone, and 27 patients who received the same regimen of verapamil ILI and who, in addition, elected to wear a FastSize Penis Extender (FastSize LLC, Aliso Viejo, CA, USA) 2–8 h per day. The authors looked at subjective improvements in curvature, and found a trend toward benefits in the combination therapy, though without statistical significance. They concluded future studies with post-treatment Doppler ultrasound were needed to objectively assess the added utility of PTT to verapamil ILI [44].

Abern et al. published such a study investigating the added utility of PTT in 2012, in which 74 men were treated with verapamil 10 mg dissolved in 10 cc NS ILI administered every other week for 24 weeks. In addition, patients were treated with oral L-arginine 1 g twice daily and oral pentoxifylline 400 mg three times daily. Finally, all patients were offered PTT, of which 39 patients decided to pursue as part of their treatment. Patients receiving PTT obtained an external penile extender (US PhysioMED, Irvine, CA, USA) and were instructed to wear the device anywhere from 2 to 8 h per day, in sessions no longer than 2 h at a time with at least 15 min between sessions. They were also instructed to add 0.5 centimeter (cm) spacers to the device every 2–3 weeks as tolerated [45].

At the end of 24 weeks, the researchers found that the patients in the PTT group, on average, wore the device for 3.3 h per day. While both groups of patients had statistically significant improvement in degree of curvature from baseline, the PTT also had a trend towards increased stretched penile length (SPL) from baseline (on average 0.3 cm, $p=0.06$), which was not observed in the non-PTT group. The authors acknowledge that selection bias and the nonrandomized nature of the study may have influenced results of the trial, and suggest a future study comparing ILI alone, to PTT alone, to ILI with PTT, would show whether ILI and PTT are synergistic in nature [45].

A retrospective review of patients treated with IFN a-2B evaluated the concomitant use of PTT (Andropenis®, [Andromedical, Spain]) with ILI-a2B. Yafi et al. examined 112 patients who had documented information regarding use of PTT. Of those patients, 31 % reported using PTT at least 2 h per day on a "regular basis." They were able to show a statistically significant gain in SPL in those patients who used PTT for greater than 3 h per day as compared to those not using PTT (4.4 mm versus 1.3 mm, $p=0.04$), concluding that PTT may offer a small but meaningful improvement in SPL if used diligently [46].

Other Therapies

One of the challenges in deciphering the numerous trials for treating PD is the large variety of combination therapies that have been employed. This highlights the fact that a definitive minimally invasive or oral treatment for the disease is yet to be discovered. Combination therapies generally combine different modalities of treatment, including oral therapies, iontophoresis, extracorporeal shock wave therapy, PTT, transdermal electromotive therapy, and topical administration therapy. Trials using multimodal therapy have generally been small, often are not randomized, and thus make it difficult to attribute benefits of therapy to a particular agent used in the treatment regimen, especially considering the natural history of the disease that can at times improve without any treatment at all. Table 22.2 lists some of the combinations therapies that have been employed.

Future Therapies

The intralesional therapies outlined in this chapter offer patients minimally invasive treatment options for treating their disease with minimal risk and beneficial, reproducible results. To this day, the gold standard for treating PD is surgery, which comes with its own set of risks both during the actual procedure (e.g., risk of anesthesia, bleeding, and infection) and in its aftermath (e.g., disease recurrence, erectile dysfunction, loss of

Table 22.2 Selected combination therapy studies for Peyronie's disease

Authors	Year	Design	*N*	Therapy	Duration	Outcomes
Paulis et al.	2013	RCT- unblinded, placebo controlled	70	Vitamin E 600 mg po daily + verapamil 10 mg ILI q 2 weeks (5 mg ILI given for the first ILI) + 5 mg verapamil iontophoresis daily + blueberry extract 160 mg po daily (36 % anthocyanosides) + propolis 600 mg po daily + topical diclofenac sodium 4 % gel bid versus above treatment without vitamin E	6 months	Statistically significant improvement in plaque size, curvature, and IIEF score (in patients with comorbidities and ED) in patients receiving vitamin E
Paulis et al.	2013	RCT- unblinded, placebo controlled	64	Peironimev-plus oral 1 tab daily + verapamil 10 mg ILI q 2 weeks + verapamil iontophoresis 5 mg 3 × week versus above treatment without oral therapy	6 months	Statistically significant improvement in penile curvature and symptom bother score in treatment arm
Mehrsai et al.	2012	RCT- unblinded	60	10 mg verapamil and 4 mg dexamethasone in 2 mL DW ILI weekly versus 10 mg verapamil and 4 mg dexamethasone in 2 mL DW TEA	6 weeks	No statistically significant improvement in plaque size, penile curvature, or erectile dysfunction. Statistically significant improvement in pain in the TEA group, greater than ILI group
Cavallini et al.	2012	RCT- single blind, placebo controlled	43	Verapamil 10 mg in 20 cc NS ILI q 2 weeks + testosterone 30 mg buccal patch bid versus verapamil ILI without testosterone replacement	6 months	Greater improvement in plaque area and penile curvature when ILI associated with testosterone supplementation
Abern et al.	2011	Nonrandomized trial- unblinded, placebo controlled	74	Verapamil 10 mg in 10 cc solution q 2 weeks + L-arginine 1 g po bid + pentoxifylline 400 mg po tid + PTT versus above with no PTT	6 months	No statistically significant improvement in PTT group versus control. Trend toward improved stretched penile length in PTT group

RCT randomized controlled trial, *ILI* intralesional injection therapy, *TEA* transdermal electromotive administration, *PTT* penile traction therapy, *IIEF* International Index of Erectile Function

sensation, loss of penile length, and device failure or erosion). The advent of stem cell therapy in the treatment of PD may someday obviate the need for surgical correction of the disease. And while "future therapies" at the time of this publication will quickly become dated, the following section aims to give readers a brief history of regenerative medicine as it pertains to PD, and, in doing so, hopefully some idea of where the field may be headed in the future.

While the promise of stem cell therapy is great, there are still many obstacles to its implementation. One basic problem is the lack of a universally accepted animal model to use in its research [47]. To date, most studies have utilized a murine model, and have used an injection of thrombin, thrombin and fibrin, or transforming growth factor beta-1 (TGF-β1) into the tunica albuginea of the study animal in order to recreate the disease [47–49]. However, researchers readily

admit that PD in humans is not completely understood and likely much more complex than our current animal models, and thus findings in these animal studies may not perfectly translate into human therapies [50].

With that being said, exciting research is taking place with regard to adipose tissue-derived stem cells (ADSCs) in the treatment of PD. ADSCs are one type of multipotent stromal cells (MSC), which can be derived from numerous other tissue sources including bone marrow, liver, muscle, amniotic fluid, placenta, umbilical cord blood, and dental pulp [51]. MSC are thought to be at least in part responsible for the regeneration of their respective tissues, a desirable property in treating a disease state characterized by abnormal tissue [48]. Specific advantages to adipose-derived MSCs (aka. ADSCs) are their abundance, their ease of harvesting, and their low processing costs [52]. In addition, ADSCs are not burdened by the ethical issues that surround the use of embryonic stem cells [48]. Finally, they have immunosuppressant properties that allow for allogeneic or even xenogeneic transplantation without creating a graft-versus-host disease [53].

An early study involving ADSCs did not pertain to PD specifically, but instead looked at how the intracavernosal injection of ADSCs may improve the endothelial and neural abnormalities responsible for hyperlipidemia-associated ED. In 2010, Huang et al. fed 28 Sprague-Dawley rats a high-fat diet that had been previously shown to induce impaired penile hemodynamics mimicking an ED state. The authors then harvested paragonadal fat in these rats, procured ADSC from this tissue, cultured it, and reinjected it into the corpus cavernosa of the treatment group of rats. They found improved erectile function in the rats treated with ADSCs, concluding that future studies were needed to look at the exact mechanism of action of the therapy, as well as the dosing, safety (especially with respect to possible increased risk of tumor formation), and durability of treatment, before human trials could even be considered [54].

In 2013, Castiglione et al. published a study evaluating the use of ADSCs in the treatment of the active phase model of PD in 12-week-old Sprague-Dawley rats. The authors separated 27 male rats into three groups, one group a sham PD model receiving ADSC treatment, one group the active PD model (via injection of TGF-β1) receiving ADSC treatment, and one group the active PD model without ADSC treatment. The authors concluded that the local injection of ADSCs prevents formation of fibrosis and elastosis in an animal model of PD. Self-described limitations to their study include an imperfect animal model, and the fact that they examined the treatment of PD in its active, inflammatory phase as opposed to the chronic state most commonly seen on presentation [52].

Also in 2013, Gokce et al. published a report looking at the use of ADSC in a rat model of PD. Again Sprague-Dawley rats (24 in total) were used, and again TGF-β1 was injected into the rat tunica albuginea in order to simulate the PD condition. The study was unique in that it had studied ADSC therapy both in the prevention and in the treatment of PD. In addition, the authors correlated their results with histological findings from tunica albuginea specimens from the sacrificed rats, concluding that in severe penile fibrosis there is increased gene expression of profibrotic tissue inhibitors of metalloproteinases (TIMPs), and decreased gene expression of antifibrotic matrix metalloproteinases (MMPs). Gokce et al. concluded that ADSCs were beneficial both in the prevention and the treatment of tunica albuginea fibrosis and erectile dysfunction in an animal model of PD [50].

AUA Update on Peyronie's Disease

In April 2015, the AUA approved new guidelines for the diagnosis and treatment of PD [55]. Within the guidelines, there were six statements specific to injection therapy of PD. Guideline Statements 8, 10, and 12 refer to the use of intralesional collagenase, interferon alpha, and verapamil in the treatment of PD, respectively. Guideline Statements 9, 11, and 13 address the need for clinicians to counsel their patients regarding the side effects of these treatments.

Guideline Statement 8 states that intralesional collagenase clostridium histolyticum may be used to treat patients with stable PD with curvature between 30° and 90°, and intact erectile function. It notes that the drug has only been studied in patients with dorsal plaques, and emphasized that collagenase does not treat pain associated with PD, or treat erectile dysfunction. It also recommends that patients be counseled regarding expectations of treatment. Specifically, the guidelines cited the IMPRESS I and II trials in which the average reduction in curvature in the collagenase treatment arm at 1 year was 17°, while the average decrease in the placebo arm at 1 year was 9.7°. The statement evidence strength of Guideline Statement 8 was Grade B, as it was based on high quality randomized controlled trials (RCTs), but the findings of the trial have yet to be reproduced.

Guideline Statement 10 deals with the use of IFN a-2b in the treatment of PD. It reads that clinicians, "may administer intralesional IFN a-2b" to PD patients, noting that, based on the single RCT, it was used on patients with stable curvature greater than 30° and without calcified plaques. It also states that IFN a-2b may be beneficial in treating curvature, plaque size, pain, and some vascular outcomes. Finally, it emphasizes that patients should be advised that average improvement in penile curvature was 13.5°. The strength of the evidence was Grade C, as the panel noted there was only one RCT of "moderate" quality and "somewhat divergent" findings in the other studies looking at treatment with interferon.

With regard to verapamil, Guideline Statement 12 gives intralesional therapy with the drug a conditional recommendation. The panel emphasizes that the majority of trials using intralesional verapamil failed to have appropriate control groups, especially considering the natural history of PD with spontaneous resolution in a minority of cases. It states clinicians should, "carefully consider" the appropriateness of this treatment modality given its uncertain efficacy and availability of other treatment that are "clearly more effective." It rates the strength of evidence Grade C, based on the conflicting findings from the two RCTs with intralesional verapamil, the lack of appropriate control groups in many of the studies, and the lack of replicated studies confirming results from the published trials.

Guideline Statements 9, 11, and 13 all consider the potential complications of the above treatments. The statements instruct clinicians to counsel patients regarding the risks of specific adverse events particular to each intralesional therapy. With regard to intralesional collagenase, Guideline Statement 9 describes common adverse events to include penile ecchymosis, penile swelling, and penile pain. These events occurred in 80.0 %, 55.0 %, and 45.4 % of patients, respectively, during the IMPRESS I and II trials. Serious adverse events occurred in 1.1 % of collagenase-treated patients during these trials, in the form of penile hematoma and corporal rupture.

The most common adverse events associated with intralesional interferon treatment include sinusitis, flu-like symptoms (e.g., fevers, chills, arthralgia), and minor penile swelling and ecchymosis. Guideline Statement 11 states these adverse events occur in 40–100 % of patients, and are self-limiting. It suggests these adverse events can be mitigated with oral hydration, and treated with over-the-counter, nonsteroidal, anti-inflammatory medications.

Finally, the potential adverse events of intralesional verapamil are perhaps the least severe and most vague. Guideline Statement 13 states that patients should be counseled regarding possible penile bruising, dizziness, nausea, and pain at the injection site.

Summary

There is much to learn about Peyronie's disease. Its true prevalence, detailed pathophysiology, and best combination of treatment even among existing therapies are all yet to be defined. Intralesional injection therapy with calcium antagonists, interferon, or collagenase clostridium histolyticum is a minimally invasive treatment modality that is proven safe and reasonably effective in the treatment of PD. Intralesional injection therapy with stem cells, while still in its infancy, offers hope for a more targeted treatment of the disease in the future.

References

1. Mulhall JP, Creech SD, Boorjian SA, Ghaly S, Kim ED, Moty A, et al. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol. 2004;171(6):2350–3.
2. Schwarzer U, Sommer F, Klotz T, Braun M, Reifenrath B, Engelmann U. The prevalence of Peyronie's disease: results of a large survey. BJU Int. 2001;88(7): 727–30.
3. Rhoden EL, Teloken C, Ting HY, Lucas ML, Teodósio da Ros C, Ary Vargas Souto C. Prevalence of Peyronie's disease in men over 50-y-old from Southern Brazil. Int J Impot Res. 2001;13(5):291–3.
4. Dunsmuir WD, Kirby RS. Francois de LaPeyronie (1678–1747): the man and the disease he described. Br J Urol. 1996;78(4):613–22.
5. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. J Urol. 2006;175(6):2115–8. discussion 2118.
6. Russell S, Steers W, McVary KT. Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. Eur Urol. 2007;51(3):640–7.
7. Moreland RB, Nehra A. Pathophysiology of Peyronie's disease. Int J Impot Res. 2002;14(5): 406–10.
8. Taylor FL, Levine LA. Non-surgical therapy of Peyronie's disease. Asian J Androl. 2008;10(1): 79–87.
9. Furey CA. Peyronie's disease: treatment by the local injection of meticortelone and hydrocortisone. J Urol. 1957;77(2):251–66.
10. Levine LA. Review of current nonsurgical management of Peyronie's disease. Int J Impot Res. 2003;15 Suppl 5:S113–20.
11. Teasley GH. Peyronie's disease; a new approach. J Urol. 1954;71(5):611–4.
12. Bodner H, Howard AH, Kaplan JH. Peyronie's disease: cortisone-hyaluronidase-hydrocortisone therapy. J Urol. 1954;72(3):400–3.
13. Desanctis PN, Furey CA. Steroid injection therapy for Peyronie's disease: a 10-year summary and review of 38 cases. J Urol. 1967;97(1):114–6.
14. Toksu E. Peyronie's disease: a method of treatment. J Urol. 1971;105(4):523–4.
15. Winter CC, Khanna R. Peyronie's disease: results with dermo-jet injection of dexamethasone. J Urol. 1975;114(6):898–900.
16. Williams G, Green NA. The non-surgical treatment of Peyronie's disease. Br J Urol. 1980;52(5):392–5.
17. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. J Urol. 1994;151(6):1522–4.
18. Roth M, Eickelberg O, Kohler E, Erne P, Block LH. Ca^{2+} channel blockers modulate metabolism of collagens within the extracellular matrix. Proc Natl Acad Sci U S A. 1996;93(11):5478–82.
19. Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. J Urol. 1997;158(4): 1395–9.
20. Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. Urology. 1998;51(4): 620–6.
21. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. J Urol. 2002;168(2):621–6.
22. Bennett NE, Guhring P, Mulhall JP. Intralesional verapamil prevents the progression of Peyronie's disease. Urology. 2007;69(6):1181–4.
23. Cavallini G, Modenini F, Vitali G. Open preliminary randomized prospective clinical trial of efficacy and safety of three different verapamil dilutions for intraplaque therapy of Peyronie's disease. Urology. 2007;69(5):950–4.
24. Shirazi M, Haghpanah AR, Badiee M, Afrasiabi MA, Haghpanah S. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. Int Urol Nephrol. 2009;41(3):467–71.
25. Soh J, Kawauchi A, Kanemitsu N, Naya Y, Ochiai A, Naitoh Y, et al. Nicardipine vs. saline injection as treatment for Peyronie's disease: a prospective, randomized, single-blind trial. J Sex Med. 2010;7(11): 3743–9.
26. Moskovic DJ, Alex B, Choi JM, Nelson CJ, Mulhall JP. Defining predictors of response to intralesional verapamil injection therapy for Peyronie's disease. BJU Int. 2011;108(9):1485–9.
27. Berookhim B, Chevinsky M, Jakubowski C, Larish Y, Nelson CJ, Mulhall JP. Ventral intralesional verapamil injections for Peyronie's disease: feasibility and safety. Abstract accepted for 20th Annual Fall Scientific Meeting of SMSNA, Miami, FL; November 20–23, 2014.
28. Duncan MR, Berman B, Nseyo UO. Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by interferons-alpha, -beta and -gamma. Scand J Urol Nephrol. 1991;25(2):89–94.
29. Wegner HE, Andresen R, Knipsel HH, Miller K. Treatment of Peyronie's disease with local interferon-alpha 2b. Eur Urol. 1995;28(3):236–40.
30. Wegner HE, Andresen R, Knispel HH, Miller K. Local interferon-alpha 2b is not an effective treatment in early-stage Peyronie's disease. Eur Urol. 1997;32(2):190–3.
31. Judge IS, Wisniewski ZS. Intralesional interferon in the treatment of Peyronie's disease: a pilot study. Br J Urol. 1997;79(1):40–2.
32. Ahuja S, Bivalacqua TJ, Case J, Vincent M, Sikka SC, Hellstrom WJ. A pilot study demonstrating clinical benefit from intralesional interferon alpha 2B in the treatment of Peyronie's disease. J Androl. 1999; 20(4):444–8.
33. Dang G, Matern R, Bivalacqua TJ, Sikka S, Hellstrom WJG. Intralesional interferon-alpha-2B injections for the treatment of Peyronie's disease. South Med J. 2004;97(1):42–6.
34. Kendirci M, Usta MF, Matern RV, Nowfar S, Sikka SC, Hellstrom WJG. The impact of intralesional

interferon alpha-2b injection therapy on penile hemodynamics in men with Peyronie's disease. J Sex Med. 2005;2(5):709–15.
35. Hellstrom WJG, Kendirci M, Matern R, Cockerham Y, Myers L, Sikka SC, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon α-2b for minimally invasive treatment for Peyronie's disease. J Urol. 2006;176(1):394–8.
36. Trost LW, Ates E, Powers M, Sikka S, Hellstrom WJG. Outcomes of intralesional interferon-α2B for the treatment of Peyronie disease. J Urol. 2013; 190(6):2194–9.
37. Gelbard MK, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. Urol Res. 1982;10(3):135–40.
38. Gelbard MK, Lindner A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. J Urol. 1985;134(2):280–3.
39. Gelbard MK, James K, Riach P, Dorey F. Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. J Urol. 1993;149(1):56–8.
40. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. J Sex Med. 2008;5(1):180–7.
41. Traynor K. Enzyme product approved for rare hand disorder. Am J Health Syst Pharm. 2010;15:416.
42. Gelbard M, Goldstein I, Hellstrom WJG, McMahon CG, Smith T, Tursi J, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. J Urol. 2013;190(1):199–207.
43. Rojo M, Iribarren IM, Rodriguez JC. Experience in the use of collagenase clostridium histolyticum in the management of Peyronie's disease: current data and future prospects. Ther Adv Urol. 2014;6(5): 192–7.
44. Abern MR, Levine LA. Intralesional verapamil injections with and without penile traction and oral therapies for management of Peyronie's disease. J Urol. 2008;179(4):408.
45. Abern MR, Larsen S, Levine LA. Combination of penile traction, intralesional verapamil, and oral therapies for Peyronie's disease. J Sex Med. 2012;9(1):288–95.
46. Yafi FA, Pinsky MR, Stewart C, Sangkum P, Ates E, Trost LW, et al. The effect of duration of penile traction therapy in patients undergoing intralesional injection therapy for Peyronie's disease. J Urol. 2015; 194(3):754–8.
47. Cerruto MA, DElia C, Molinari A, Cavicchioli FM, D'Amico A, Artibani W. Animal experimental model of Peyronie's disease: a pilot study. Arch Ital Urol Androl. 2013;85(1):28–33.
48. Davila HH, Ferrini MG, Rajfer J, Gonzalez-Cadavid NF. Fibrin as an inducer of fibrosis in the tunica albuginea of the rat: a new animal model of Peyronie's disease. BJU Int. 2003;91(9):830–8.
49. El-Sakka AI, Hassan MU, Nunes L. Histological and ultrastructural alterations in an animal model of Peyronie's disease. Br J Urol. 1998;81(3):445–52.
50. Gokce A, Abd Elmageed ZY, Lasker GF, Bouljihad M, Kim H, Trost LW, et al. Adipose tissue-derived stem cell therapy for prevention and treatment of erectile dysfunction in a rat model of Peyronie's disease. Andrology. 2014;2(2):244–51.
51. Albersen M, Kendirci M, Van der Aa F, Hellstrom WJG, Lue TF, Spees JL. Multipotent stromal cell therapy for cavernous nerve injury-induced erectile dysfunction. J Sex Med. 2012;9(2):385–403.
52. Castiglione F, Hedlund P, Van der Aa F, Bivalacqua TJ, Rigatti P, Van Poppel H, et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease. Eur Urol. 2013;63(3):551–60.
53. Lin C-S, Lin G, Lue TF. Allogeneic and xenogeneic transplantation of adipose-derived stem cells in immunocompetent recipients without immunosuppressants. Stem Cells Dev. 2012;21(15):2770–8.
54. Huang Y-C, Ning H, Shindel AW, Fandel TM, Lin G, Harraz AM, et al. The effect of intracavernous injection of adipose tissue-derived stem cells on hyperlipidemia-associated erectile dysfunction in a rat model. J Sex Med. 2010;7(4 Pt 1):1391–400.
55. Nehra A, Alterowitz R, Culkin DJ, Faraday MM, Hakim LS, Heidelbaugh JJ, et al. Peyronie's disease. J Urol. 2015;194(3):745–53.

Peyronie's Disease: Surgical Therapy

23

Lorenzo DiGiorgio and Hossein Sadeghi-Nejad

Overview and Historical Perspective

Peyronie's disease is an anatomic deformity that causes abnormal penile curvature, undesired cosmetic appearance, erectile dysfunction, painful erections, and much psychological strife for many men. It is defined by scarring and plaque formation of the anatomy of the tunica albuginea of the penis. The earliest descriptions of the condition in the Western literature are attributed to Guilielmus of Salicetum (1210–1276) and Theodoric Borgognoni (1205–1298) who are said to have described penile curvature in medical and anatomical textbooks. Gabriele Falloppio described Peyronie's disease in *Observationes anatomicae* during his time as professor and chair of anatomy and surgery at the University of Padua. Falloppio was a major contributor to the field of anatomy most notably male and female reproductive organs [1]. It was not until 1743 though that the disease process was coined Peyronie's. François Gigot de la Peyronie was credited with describing the penile disorder after examination of an erect penis with upward curvature. What he found was an induration of the corpora cavernosa that he described as "rosary beads of scar tissue" [2].

Peyronie's disease is likely to be well under reported. The symptomatic incidence is approximately 1–5 % while asymptomatic incidence is 0.4–1 %. Newer reviews found the prevalence can be as high as 8.9 % [3]. The disease usually manifests in middle age men with an average age of 53 years. Schwarzer and colleagues [4] published the results of a questionnaire based on the response of 8000 men with a 55.4 % response rate. This population based cohort consisted of men living in Germany aged 30–80 years old. The authors found a prevalence of 3.2 % for the new appearance of a palpable plaque. The prevalence by age was 1.5 % for men aged 30–39 years, 3 % for men aged 40–49 years, 3 % for men aged 50–59 years, 4 % for men aged 60–69 years, and 6.5 % for men aged 70 or older. In addition, 84 % of males reported penile angulation and 47 % reported painful erections. A triad of plaque, angulation, and pain was reported in 32 % whereas 41 % reported ED.

The disease process has been separated into two different phases. The first is an "active"

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phase or a time of inflammatory changes usually associated with painful erections and worsening deformity. The second is the "inactive" or quiescent phase which is characterized by stability of disease and stable plaque deformity. Kadioglu et al. [5] have reported characteristics from 307 men with PD, of whom 63 patients opted for no treatment and presented for follow-up. In that group, 67 % of men had no change in deformity, 30 % progressed and 3 % reported complete improvement.

There have been many proposed associations with Peyronie's including but not limited to beta blockers and phenytoin, PDE5 inhibitors, and intracavernosal injections for erectile dysfunction, external genitalia trauma or buckling injury during sexual intercourse with a resultant inflammatory reaction and fibrosis, urethral instrumentation or trauma, diabetes mellitus, tympanosclerosis, plantar fascial contracture, and Paget's disease [6, 7]. The only consistent link has been with Dupuytren's contracture which is seen in 30–40 % of men with Peyronie's disease no other association has been confirmed.

During the active phase medical treatments have focused on plaque disruption, plaque dissolution, immune system modulation, reducing inflammation, and reducing oxidant stress very early in the disease course prior to the onset of plaque fibrosis and calcification that typically occurs after 1–2 years. Some of the medical therapies that have been used for the treatment of PD include oral preparations, such as vitamin E, colchicine, para-aminobenzoate, tamoxifen, carnitine, or various herbal preparations. Topical therapies include intralesional injection therapy with verapamil, collagenase, interferon alpha-2b or corticosteroids as well as extragenital therapies with shock-wave lithotripsy, short-wave diathermy, laser therapy, and ultrasound or radiation therapy [8–19]. In the recent AUA guideline it has been noted that a few of the above oral therapies are without efficacy and are not recommended in the treatment plan. It is proposed that they may delay the use of more potent treatment options. Those not recommended include vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine. It should also be noted that ESWT or RT is not recommended at this time but may benefit patients found to have pain associated with Peyronie's. Surgical therapy has been reserved for men who have failed medical treatment and are found to be in the quiescent phase of the disease process.

Penile Anatomy and Pathophysiology

A brief review of penile anatomy is essential in understanding the pathophysiology and surgical correction of Peyronie's disease. Beneath the skin is the dartos fascia which overlies Bucks fascia. Contained in Buck's fascia is a single corpus spongiosum lying ventrally between the paired corpora cavernosa. The corpora cavernosum is an intricate network of capillaries which supply the blood flow necessary for erection. The corpora cavernosa are covered by a thick lining of connective tissue known as the tunica albuginea. This is a thick tissue composed of mostly Type I collagen and to a lesser degree elastin, Type III and IV collagen. This combination provides elasticity and strength.

There have been many proposed etiologies which include mechanical stress, microvascular trauma, and inflammatory pathways. The pathophysiology is poorly understood and likely is related to a combination of factors. It has been shown that excessive bending during erection or blunt trauma to the erect penis may result in bleeding into the subtunical spaces or delamination of the tunica at its point of attachment to the inner circular layer of the tunica albuguinea, with resultant accumulation of fibrinogen, fibrin, and clot in the subtunical layers and subsequent initiation of an inflammatory reaction [20]. This is then followed by the recruitment of inflammatory cells (neutrophils, platelets, and macrophages) and subsequent release of various cytokines, autocoids, and vasoactive factors that induce a fibrotic reaction [21, 22].

Patient Presentation and Evaluation

The most common presenting symptom is penile deformity and can be found in 94 % of patients with Peyronie's disease. Less commonly patients present with penile pain or penile lump which account for 40 and 21 % respectively [23]. Evaluation of the Peyronie's patient should begin with a thorough history and physical exam. History should focus on timing of onset, prior penile surgery, urethral instrumentation, trauma, and comorbid disease including Dupuytren disease. It is also important to focus on causes of erectile dysfunction such as vascular disease and diabetes mellitus as most Peyronie's patients will have report some element of erectile dysfunction. Physical exam of the penis and hands to elicit any element of Dupuytren is essential. The penis should be examined on stretch and length should also be documented. It is also prudent to have patient bring photographs of his erect penis to identify the direction and degree of curvature. Radiographic images may demonstrate calcified plaques but more commonly used is penile duplex Doppler ultrasound with pharmacologic challenge. Ultrasound in combination with pharmacologic stimulation (i.e., intracavernosal alprostadil injection) is useful for documenting hemodynamics, complexity of curvature, erectile function and can demonstrate the size and location of the plaque in relation to the corpora cavernosa.

Surgical Management

In deciding the treatment for this disease appropriate patient selection is paramount. As discussed above there are two phases of disease. Medical therapy should be employed during the active phase. Once the patient has formed a stable plaque the disease has entered the quiescent phase. Stable disease is defined as the state in which the deformity is no longer progressive and the symptoms have been clinically unchanged for at least 3 months. Surgical management is reserved to correct the deformity and either restore or preserve erectile function. Refer to Fig. 23.1 for treatment guidelines. A number of surgical techniques have been devised and modified for the correction of this disease.

Nesbit Procedure

First described in 1965 for congenital curvature and later in 1977 for Peyronie's disease the Nesbit procedure has been a longtime technique in the urologist repertoire. There have been many modifications over the years from the originally described procedure. These modifications have increased patient satisfaction rates and have increased the simplicity of the procedure. The procedure entails a subcoronal incision followed by degloving of the penis to its base. A small piece of tunica opposite the plaque and angulation is then excised and the tunica defect is closed. Finally Bucks fascia is closed over the corporotomy site [24, 25]. As discussed many modifications have been made to the initial description of the Nesbit procedure and will be discussed below. Licht et al. looked at data on 30 patients who had undergone a modified Nesbit procedure which was compared to patients who had undergone either a standard Nesbit procedure or plaque excision with synthetic patch grafting by the same group of surgeons. The modified Nesbit procedure showed no statistically significant difference in penile curvature elimination, patient satisfaction, rates of postoperative impotence or need for subsequent surgery. However, there was an overall higher rate of penile curvature elimination (79–93 %) and patient satisfaction (79–83 %) when compared to standard Nesbit procedure [26]. The largest drawback of the Nesbit and modified Nesbit procedures is the perceived penile shortening. Also of concern is erectile dysfunction and reoccurrence. It is sometimes difficult to assess "penile shortening" as many patient affected by Peyronie's already perceive shortening. In actuality many of the studies show that

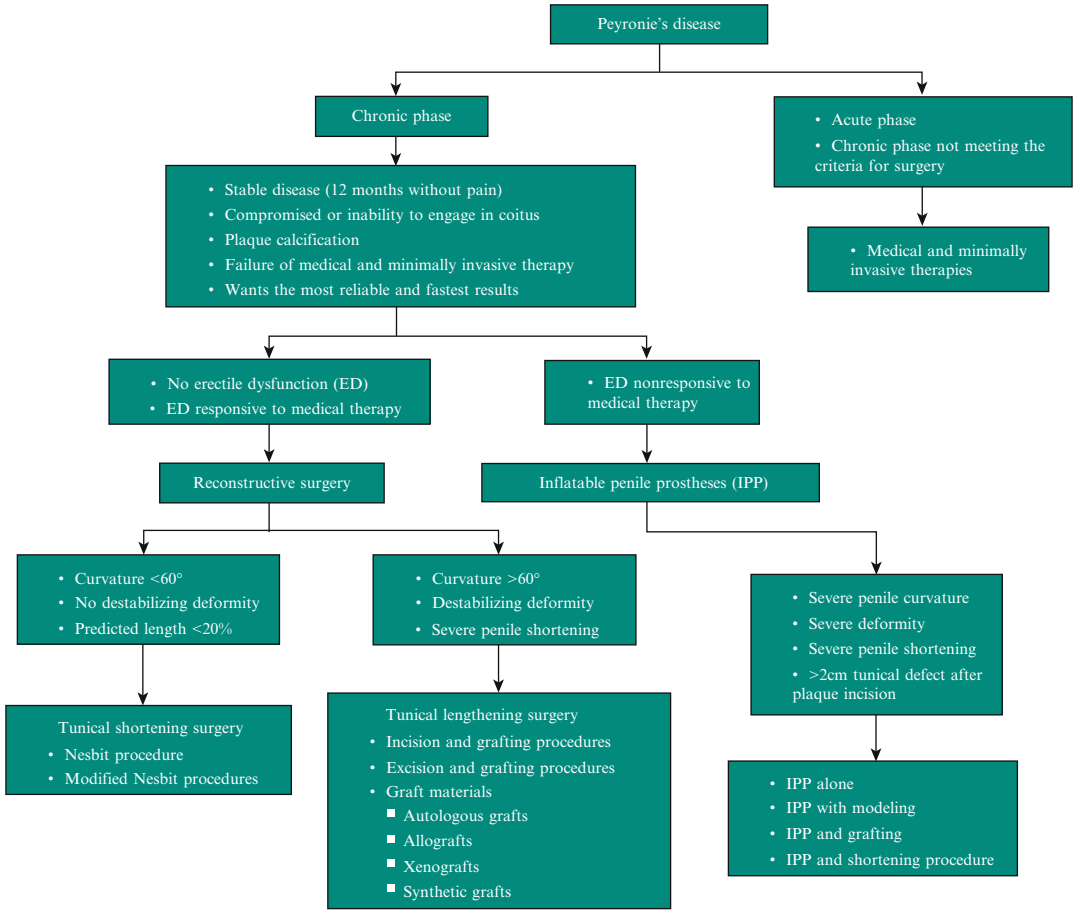

Fig. 23.1 Surgical algorithm for patients with chronic phase PD. *IPP* inflatable penile prostheses (Used with permission from Carson CC, Levine L. Outcomes of surgical treatment of Peyronie's disease. BJUI 2014; 113: 704–713)

there is no objective shortening in many of these cases. In one of the largest studies ever conducted 359 men with Peyronie's disease underwent the Nesbit procedure. Of those men only 17 had significant shortening, defined as greater than 2 cm. Of those 17, five have already undergone a Nesbit operation and only six had problems with sexual intercourse [24]. Rolle et al. reviewed 50 patients undergoing the Nesbit procedure for either congenital curvature or Peyronie's disease. They found that of the Peyronie's' disease subgroup 14/18 complained of penile shortening while only three patients were unsatisfied due to shortening. Regarding erectile satisfaction International Index of Erectile Function 5 scores improved with statistical significance from an average of 17.83 ± 4.17, whereas postoperatively it was 19 ± 4.63 [25]. As these studies demonstrate perceived penile shortening is inevitable but most importantly patients are happy and satisfied with the results. What you cannot argue is that in the Nesbitt and procedures like the Nesbit, there is no restoring or lengthening offered.

Summary Points

- Nesbit and modified Nesbit procedures are used for males with mild–moderate curvature and adequate penile length.
- These procedures show excellent patient and patient partner satisfaction scores.
- Perceived penile shortening is seen in a high percentage of patients undergoing this procedure.

Plication Technique

Plication surgery does not require excision or incision of the healthy tunica albuginea. The tunica opposite the site of plaque and angulation is sutured in a transverse fashion thus eliminating the penile curvature. By incising Buck's fascia the neurovascular bundles can be visualized and avoided. Popularized by Essed and Schroeder in 1998 when they described placing non-adorable sutures in an ellipse fashion contralateral to the plaque. When passed through Buck's fascia and tied down they straighten the penis [27]. Commonly a "16 dot" technique is used (Fig. 23.2a, b). Every four dots refer to placement of one suture. Points of suture entry and exit should be placed approximately 1 cm from each other and 2–3 cm lateral to the corpus spongiosum. These methods can be modified based on the location and degree of curvature. In a large review of 132 patients undergoing the "16 dot" technique Gholami et al. found 93 % reported straightening while the other 7 % complained of a slight curvature and only 3 % complained of worse erectile function. Most common complaint not unsurprisingly was penile shortening, but this was only documented in 41 % of patients [28]. Another technique employed by Yachia is making a longitudinal incision in the tunica followed by horizontal closure avoiding excision of tunica. This would lead to a reduction in the injury to the neurovascular bundle and glans hypoesthesia that is sometimes seen post Nesbit procedures [29]. Lopes et al. conducted a large retrospective review of patients who underwent Yachia

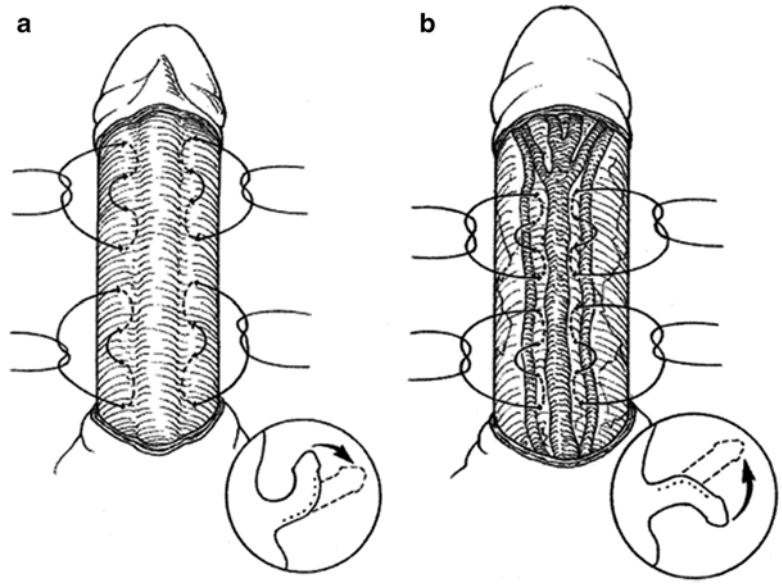

Fig. 23.2 (**a**, **b**) 16-Dot Procedure: Planned suture entry sites marked with pen. Erection attained throughout operation with papaverine. (**a**) 16-Dot repair of ventral curvature. Peridorsal vein sutures without dissection of neurovascular bundles. (**b**) 16-Dot repair of dorsal curvature with periurethral sutures of 2-0 Ticron (All used with permission from Gholami S, Lue T. Correction of Penile Curvature Using the 16-DOT Plication Technique: A review of 132 Patients. Journal of Urology 2002;167:2066–2069)

corporoplasty. They found 88.4 % of 117 patients reported excellent satisfaction. In this large review all patients reported perceived penile shortening but only three reported this as a cause of sexual dysfunction [30]. Other complications of plication technique include pain from the suture, pain with erection, decreased penile sensation and hematoma. Non-absorbable sutures should be used and patient should be aware that he may feel a small bump where the suture is tied. Similar to the Nesbit procedure this technique is reserved for a select group of patients. This procedure is reserved for the less complex curvatures and patients with adequate penile length. One advantage of this procedure is the ability to perform under local anesthesia. It has limited morbidity and can be completed quickly, it does not preclude from doing more extensive surgery in the future if there is a return of curvature.

Summary Points

- Plication techniques are typically reserved for those men with mild–moderate curvature and adequate penile length. The authors have had excellent results using the 16 dot technique for curvatures as much as 90°. Placement of a small, 2–3 mm incision in the tunica at suture entry points is a simple modification that allows burial of the knot to minimize uncomfortable sensation of the knot by the patient.
- Postoperative complications may include: penile shortening, impotence, loss of penile sensation, and palpable knots at suture site.
- Procedure can be performed under local anesthesia with a short operative time.

Incision/Excision Techniques

Plaque incision/excision techniques are reserved for more complex deformities. Patients with hourglass deformity, large ventral/dorsal curvatures (>60°), those with large plaque deformities and those with inadequate length benefit most from this surgical option. The procedure broken down to its simplest components are removal of the diseased tissue with replacement with a graft

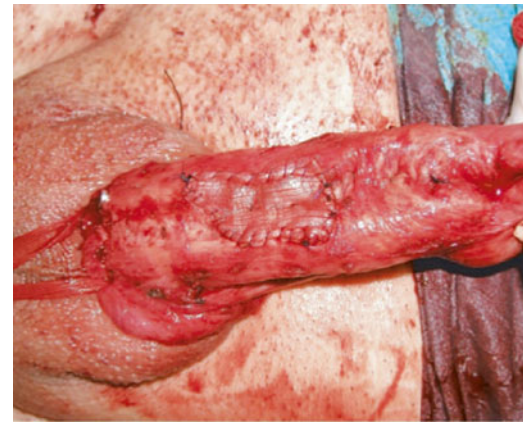

Fig. 23.3 Plaque excision and vein grafting (Used with permission from Tsafrakidis P, Blake C, Pearcy R, Persad R. Peyronie's disease. Trends Urology, Gynecol. Sexual Health 2009; 14: 17–21)

of surgeon's choice (Fig. 23.3). Grafting material will be discussed later in this chapter. The incision technique involves making of multiple corporotomy defects and replacing these scarred areas with more pliable tissue. These techniques are sometimes referred to as tunical lengthening procedure. They carry a higher rate of erectile dysfunction but serves as excellent strategies for straightening in the more complex patient. The more tissue excised leads to increased rates of postoperative erectile dysfunction as the venoocclusive mechanism is disrupted with excision techniques. The success rates seem to be variable among the different grafts used.

Grafts fall under one of four categories, autologous, allografts, xenografts, or synthetic. Autologous grafts include temporalis fascia, tunica vaginalis, penile skin "islands" and vein grafts to name a few. Venous grafting has moved to the forefront of these options. ElSakka reported the use of deep dorsal vein grafts but this later was found to not provide enough donor tissue. For this reason saphenous vein grafting has become the predominant vein of choice. In one study of 112 patients with saphenous vein graft there was 92 % satisfaction rate this compares to 58 % with rectus sheath and 88 % with dermal grafting [31–33]. Straightening rates were high in all these procedures with venous grafting having 96 % rate of straightening. Oral mucosa has also

been used with promising results. Buccal mucosal grafts, also used for urethroplasty, offer an elastic and reduced contracture rate. From this Saleem proposed the use of lingual mucosal grafts as they report similar efficacy and lower graft site complications [34]. The risk of comorbidities associated with autologous grafting must be considered in any grafting procedure.

Allografts and xenografts have moved forward in their use in the surgical world. Some of the more common material used is small intestinal mucosa, fascia lata, and pericardium. Whether from cadaveric or bovine donors the data are variable but both are viable options with further research needed in comparison studies. Synthetic grafts (Gortex and Dacron) have been limited by their perigraft fibrosis, substantial postoperative inflammation around the grafted site with subsequent recapitulation of the plaque and possible further curvature [35]. It is important to remember grafting techniques are reserved for the most complex of Peyronie's disease patients. At 5 year follow up studies the satisfaction scores decreased from 86 to 60 % due to ED (22.5 %) and penile shortening (35 %) [17, 36]. Perceived penile shortening was reported in 40 % of patients. However, there were no differences between the mean preoperative penile length and the 32 month postoperative measured penile lengths [37].

Summary Points

- Incision or excision is the surgical technique preferred for more complex deformities, inadequate penile length or large plaque deformities. The authors prefer to avoid plaque excision and the need for grafting whenever possible and have had excellent success with the plication procedures without excision/grafting for curvatures as severe as 90°. Avoidance of plaque excision/grafting has the advantage of lower chances of long-term erectile dysfunction and/or sensory deficits due to nerve damage.
- Patient satisfaction scores drop off at 5 years due to erectile dysfunction and penile shortening.
- When grafts are indicated, processed/sterilized cadaveric pericardium (i.e., Tutoplast, Bard) may be used.

Penile Prosthesis

It is estimated that 20–30 % of patients with Peyronie's disease also suffer from concomitant erectile dysfunction. The etiology of erectile dysfunction in this patient population may be direct results of veno-occlusive disease (83.9 %) or secondary to arterial blood flow anomalies (48.2 %) [38]. For men with PD who suffer from concomitant ED, penile prosthesis surgery can achieve penile straightening through mechanical stretching of the fibrotic tunica albuginea lining the corpora and simultaneously providing a rigid penis for satisfactory sexual intercourse. Penile remodeling has been well documented since the late 1980s. Penile remodeling involves forcible counter flexion in the opposite direction of the curvature causing rupture of the fibrotic plaque. Wilson et al. describe their remodeling technique which involves cross clamping of the cylinders with maximal distention of the corporal cylinders. This effectively prevents pump damage from excessive back pressure. The modeling position is held for 90 s and then additional fluid is added to the cylinders and repeated for another 90 s [39]. It is important to note that remodeling technique was not possible until the introduction of inflatable prosthesis devices that provided enough rigidity against deformity to act as a fulcrum for disrupting the plaque. Two modeling sessions are usually adequate and if a residual curvature of greater than 20° is noted, incision of the central portion of the plaque may be carried out down to the exposed cylinder with modeling repeated, a Nesbit or graft procedure performed [40]. Complications related to penile prosthesis insertion with modeling may include urethral perforation (3 %), prosthesis infection (3 %), and failure of modeling (8 %). The two most commonly used penile prostheses used to treat Peyronie's disease are American Medical System 700™ CX (Marlborough, MA) and the Coloplast Titan®

(Minneapolis, MN). In a comparison study of both models Chung et al. found excellent patient satisfaction with both. Of the patients surveyed after procedure 79 % of patients scored 4/5 of overall satisfaction and 82 % would undergo the operation again and recommended inflatable penile prosthesis to others [41]. This treatment modality can also be combined with the above procedures to remedy the most complex Peyronie's disease. In a retrospective review done by Chung et al. they found excellent results in patients that underwent inflatable penile prosthesis surgery with synchronous penile plication. All 15 patients who responded to postsurgical surveys reported improvement in curvature and erections adequate for sexual intercourse. Although 11/15 reported penile shortening all 15 reported improvement in their condition [42]. Inflatable penile prosthesis has been shown to have excellent results for patients with Peyronie's and concomitant erectile dysfunction. It is an excellent treatment option and when combined with either grafting or Nesbit procedure can treat a wide variety of the Peyronie's population. See Fig. 23.4a–c.

Summary Points

- Penile Prosthesis implantation is the optimal treatment modality in men with erectile dysfunction and Peyronie's disease.
- Penile straightening can be achieved in 86–100 % of patients by employing penile prosthesis insertion with modeling, plaque incision, and PTFE graft. In the authors' experience, the combination of modeling and implant placement has been effective in all cases and grafting has not been necessary.
- The technique of modeling carries the risk of urethral perforation (3 %), prosthesis infection (3 %), and failure of modeling (8 %).
- Either Coloplast Titan or American Medical System 700CX show equivalent patient satisfaction rates as inflatable prosthesis for this patient population.

Postoperative Care

Penile rehab after surgery has been proposed to assist with the healing process and promote erectile function. Rehabilitation is not a new

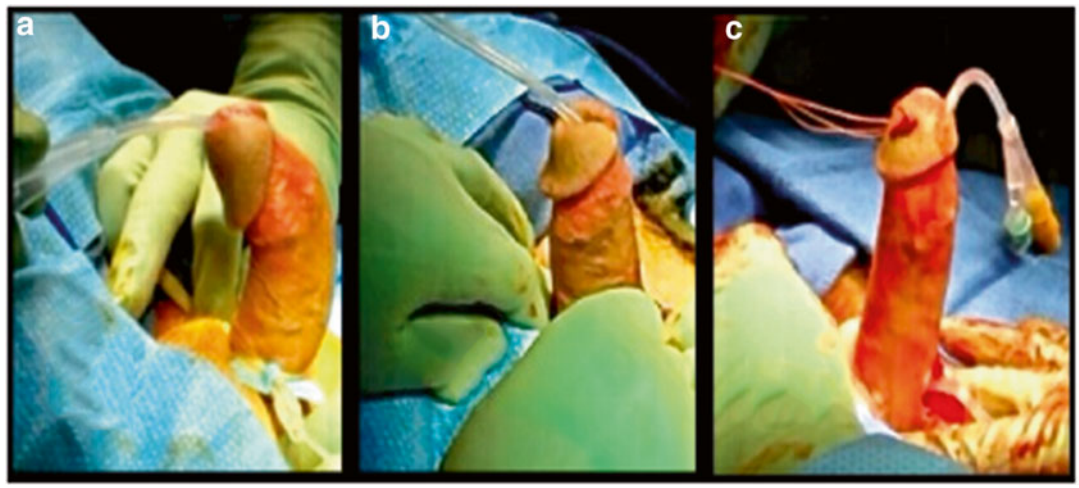

Fig. 23.4 (**a**–**c**) Penile appearance (**a**) before plication, (**b**) after plication, and (**c**) after inflatable penile prosthesis (IPP) insertion reveals complete correction of dorsal Peyronie's curvature with plication and correction of erectile dysfunction (ED) with implant (All used with permission from Chung P, Scott J, Morey A. High Patient Satisfaction of Inflatable Penile Prosthesis Insertion with Synchronous Penile Plication for Erectile Dysfunction and Peyronie's Disease. Journal of Sexual Medicine 2014; 11: 1593–598)

concept and has been used is post radical prostatectomy in patients to help with erectile problems some patients may see after that surgery. Rehab includes manual therapy as well as pharmacologic intervention. It has been suggested that massage and stretching techniques to be performed 2 weeks after surgery. Carson and Levine have also a suggested 6-week course of bedtime phosphodiesterase inhibitor therapy is also recommended and should be initiated 7–10 days after surgery [43]. It is also postulated that vacuum erection device can be used to prevent graft shrinkage, penile shortening, and recurvature.

Conclusion

Peyronie's disease is one that affects a large population of men. The exact prevalence is unknown as it can be a difficult topic for men to discuss with their doctors. Early in the disease process medical and noninvasive treatments have been used with variable success rates. Even fewer patients have spontaneous resolution of their disease process. Most men with the disease will enter a stable phase where surgery becomes a possible curative measure. Throughout the years a variety of surgical procedures have been used to manage the variety of disease presentations. The armamentarium of the urologist must include techniques tailored to each patient. The various modifications of the original Nesbit procedure have proven excellent treatments for a select group of patients. This includes those with <60 % curvature, adequate penile length, no hourglass deformity and good preoperative erectile function. Grafting procedures are reserved for the most complex curvatures, and the high rate of post-op erectile dysfunction must be discussed. There is a multitude of grafts available with variable results. The use of lingual grafts and xenografts are promising. Synthetic grafts seem to cause the most complications and their use should be only in rare cases. Penile implants are unique in that they can be used to cure patients that suffer from Peyronie's and erectile dysfunction. The procedures discussed above can be combined to cure the vast population of Peyronie's disease patients. Each technique when applied to the correct patient offers excellent results.

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References

1. Musitelli S, Bossi M, Jallous H. A brief historical survey of "Peyronie's disease". J Sex Med. 2008;5(7):1737–46.
2. de la Peyronie F. Sur quelques obstacles qui s'opposent a l'ejaculation naturelle de la semence. Memoir'Acad Chirurg. 1743;1:318.
3. Mulhall J, et al. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol. 2004;171:2350–3.
4. Schwarzer U, Sommer F, Klotz T, Braun M, Reifenrath B, Engelmann U. The prevalence of Peyronie's disease: results of a large survey. BJU Int. 2001;88(7):727–30.
5. Kadioglu A, et al. A retrospective review of 307 men with Peyronie's disease. J Urol. 2002;168:1075–9.
6. Devine CJ, Somers KD, Jordan SG, Schlossberg SM. Proposal: trauma as the cause of the Peyronie's lesion. J Urol. 1997;157:285–90.
7. Carson CC, Jordan GH, Gelbard MK. Peyronie's disease: new concepts in etiology, diagnosis and treatment. Contemp Urol. 1999;11:44–64.
8. Pryor JP, Farrell CR. Controlled clinical trial of vitamin E in Peyronie's disease. Progr Reprod Biol Med. 1983;9:41–5.
9. Akkus E, Carrier S, Rehman J, et al. Is colchicine effective in Peyronie's disease? A pilot study. Urology. 1994;44:291–5.
10. Hasche-Klunder R. Treatment of Peyronie's disease with para-aminobenzoacidic potassium (Potaba). Urology. 1978;17:224–7.
11. Weidner W, Hauck EW, Schnitker J. Peyronie's disease Study Group of Andrological Group of German Urologists: potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease – a prospective, placebo-controlled, randomized study. Eur Urol. 2005;47:530–6.
12. Biagiotti G, Cavallini G. Acetyl-l-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. BJU Int. 2001;88:63–7.
13. Cavallini G, Biagiotti G, Koverech A, Vitali G. Oral propionyl-l-carnitine and intraplaque verapamil in the therapy of advanced and resistant Peyronie's disease. BJU Int. 2002;89:895–900.

14. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. J Urol. 2002;168:621–5. Discussion 625–626.
15. Gelbard MK, James K, Riach JN, Dorey F. Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. J Urol. 1993;149:56–8.
16. Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single center, non-placebo-controlled study. J Sex Med. 2007;5(1):180–7.
17. Hakim LS, Khater U. Non-surgical management of Peyronie's curvature: experience using intralesional Intron-A therapy [abstract 72]. J Sex Med. 2004;1:51.
18. Bodner H, Howard AH, Kaplan JH. Peyronie's disease: cortisone-hyaluronidase-hydrocortisone therapy. J Urol. 1954;72:400–3.
19. Butz M, Teichert HM. Treatment of Peyronie's disease by extracorporeal shock waves abstract. J Urol. 1998;159(Suppl):118.
20. Moreland RB, Nehra A. Pathophysiology of Peyronie's disease. Int J Impot Res. 2002;14:406–10.
21. Van de Water L. Mechanisms by which fibrin and fibronectin appear in healing wounds: implications for Peyronie's disease. J Urol. 1997;157:306–10.
22. Somers KD, Dawson DM. Fibrin deposition in Peyronie's disease plaque. J Urol. 1997;157:311–5.
23. Pryor JP, Ralph DJ. Clinical presentation of Peyronie's disease. Int J Impot Res. 2002;14:414–7.
24. Ralph DJ, et al. The Nebit operation for Peyronie's disease: 16 year experience. J Urol. 1995;154(4): 1362–3.
25. Rolle L, et al. The Nesbit operation for penile curvature: an easy and effective technical modification. J Urol. 2005;173(1):173–4.
26. Licht M, et al. Modified Nesbit procedure for the treatment of Peyronie's disease: a comparative outcome analysis. J Urol. 1997;158:460–3.
27. Essed E, Schroeder FH. New surgical treatment for Peyronie's disease. Urology. 1985;25:582.
28. Gholami S, Lue T. Correction of penile curvature using the 16-DOT plication technique: a review of 132 patients. J Urol. 2002;167:2066–9.
29. Yachia D. Modified corporoplasty for the treatment of penile curvature. J Urol. 1990;143:80–2.
30. Lopes I, et al. Penile corporoplasty with Yachia's technique for Peyronie's disease: single center experience with 117 patients. Urol Ann. 2013;5:167–71.
31. Craatz S, et al. The dorsal lamina of the rectus sheath: a suitable grafting material for the penile tunica albuginea in Peyronie's disease? BJU Int. 2006;97: 134–7.
32. Goyal NK, et al. Experience with plaque excision and dermal grafting in the surgical treatment of Peyronie's disease. Singapore Med J. 2008;49:805–8.
33. ElSakka AI, et al. Venous patch graft for Peyronie's disease. Part II: outcome analysis. J Urol. 1998;160: 2050–3.
34. Salem E, Elkady E, et al. Lingual mucosal graft treatment of Peyronie's disease. Urology. 2014;84(6): 1374–7.
35. Carson CC, Chun JL. Peyronie's disease: surgical management: autologous materials. J Sex Med. 2012;14(5):329–35.
36. Kalsi J, et al. The results of plaque incision and venous grafting (Lue procedure) to correct the penile deformity of Peyronie's disease. BJU Int. 2005;95(7): 1029–33.
37. Montorsi F, et al. Evidence based assessment of long-term results of plaque incision and vein grafting for Peyronie's disease. J Urol. 2000;163(6):1704–8.
38. Carson GC. Penile prosthesis implantation in the treatment of Peyronie's disease and erectile dysfunction. Int J Impot Res. 2000;12:S122–6.
39. Wilson SK, Delk II JR. A new treatment for Peyronie's disease: modeling the penis over an inflatable penile prosthesis. J Urol. 1994;152:1121–3.
40. Mulcahy JJ, Wilson SK. Management of Peyronie's disease with penile prostheses. Int J Impot Res. 2002;14:384–8.
41. Chung E. Comparison between AMS 700 CX and coloplast titan inflatable penile prosthesis for Peyronie's disease treatment and remodeling: clinical outcomes and patient satisfaction. J Sex Med. 2013;10:2855–60.
42. Chung P, Scott J, Morey A. High patient satisfaction of inflatable penile prosthesis insertion with synchronous penile plication for erectile dysfunction and Peyronie's disease. J Sex Med. 2014;11:1593–8.
43. Carson CC, Levine L. Outcomes of surgical treatment of Peyronie's disease. BJU Int. 2014;113:704–13.

Management of Priapism

24

Brian V. Le and Arthur L. Burnett

Introduction

Priapism is an uncommon pathologic condition of the penis resulting in prolonged penile erection in the absence of sexual arousal and desire. The etymology of the term comes from the Greek origin of Priapus, the god of fertility [1]. The clinical signs and symptoms of priapism are a persistent erection lasting many hours, and may be accompanied by pain, swelling, and skin changes depending on the etiology. There are three major subtypes of priapism: ischemic, recurrent ischemic, and nonischemic. The common presentation of a persistent erection belies a fundamental difference in the pathogenesis, management, and urgency of these subtypes.

While nonischemic priapism may present as a painless, persistent erection—it is not considered a medical emergency as oxygenated blood continues to flow to the penis [2]. Classically, its presentation is that of a recurrent condition associated with a prior history of pelvic trauma or radiation. Patients are rarely in distress. Ischemic priapism in contrast is a medical emergency and is associated with tissue necrosis and fibrosis. These complications are exacerbated the longer the condition is left untreated. Thus, timely diagnosis and management are critical to reduce the sequelae of cavernosal tissue ischemia. Patients typically present in moderate distress with localizing pain to the penis. They may report a history of recent pharmaceutical or recreational drug usage, and may delay seeking treatment out of embarrassment [3]. This chapter focuses on the diagnosis and management of priapism in the clinical setting with an emphasis on ischemic priapism.

Erection Physiology

To understand the pathogenesis of an abnormal and prolonged erection, we must first review the current understanding of the normal erection pathway. At baseline, a complex balance between flaccidity and erection is maintained through opposing inputs of vasorelaxation and vasoconstriction from the parasympathetic and sympathetic system [4]. When the penis is flaccid, the vascular and smooth muscle tone is maintained through various vasoconstrictive factors including,

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but not limited to, Rho kinase and phosphodiesterase type 5 (PDE5) [5]. This tonic contractile state may be inhibited with genital stimulation, psychosexual excitement, or rapid eye movement sleep [6]. When penile erection is induced, there is smooth muscle relaxation of the cavernosal arteries through a nitric oxide-dependent pathway, allowing for increased arterial blood flow leading to cavernosal tissue engorgement. This engorgement subsequently compresses venous outflow sustaining the erectile response [7]. The nature of the nitric oxide (NO) signaling pathway involved in erection physiology has been an area of intense study over the past several decades. It has been revealed that erection stimulation involves vascular and neurogenic pathways regulated by endothelial and neuronal isoforms of the NO synthase enzyme, the primary mediator of NO synthesis. These enzymes catalyze the conversion of L-arginine to NO, which diffuses locally and stimulates cGMP-dependent vasodilation [8]. Termination of the response occurs with hydrolysis of cGMP by PDE5, returning the penis to the flaccid state [9].

Classification of Priapism

Classification of priapism provides a framework for evaluation, management, and study of these disorders. There are three main subtypes of priapism: ischemic, recurrent ischemic, and nonischemic.

Ischemic Priapism

Ischemic priapism, also known as low flow or veno-occlusive priapism, is the most common presentation of priapism with 95 % of presentations being ischemic in nature [10, 11]. It is characterized by absent or low cavernous blood flow, tenderness to palpation, and rigidity. This reflects a compartment-like syndrome with compression of the venous sinusoids preventing drainage [2, 12]. A variety of etiologies have been described, including neurologic conditions, pharmacologic exposures, trauma, spider bites, hematologic disorders, and idiopathic presentations. A more extensive list of etiologies is provided in Table 24.1.

Table 24.1 Causes of priapism

Etiology	Examples
Hematologic disorders	Sickle cell disease, thalassemia, glucose-6-phosphate dehydrogenase
Medications	Vasoactive erectile agents (papaverine, phentolamine, prostaglandin E1, combination therapy), alpha-adrenergic receptor antagonists (prazosin, terazosin, tamsulosin) antianxiety agents (hydroxyzine), anticoagulants (heparin, warfarin), antidepressants and antipsychotics (trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thioridazine, phenothiazines, antihypertensives (hydralazine, guanethidine, propranolol)
Recreational drugs	Alcohol, cocaine, marijuana
Hormones	Gonadotropin-releasing hormone, testosterone
Infectious/venom	Scorpion sting, spider bite, rabies, malaria
Metabolic	Amyloidosis, Fabry disease, gout
Neoplastic (regional infiltration or metastatic)	Kidney, bladder, prostate, urethra, penis, testis, colorectal, lung
Neurogenic	Syphilis, spinal cord injury, cauda equina syndrome, autonomic neuropathy, lumbar disc herniation, spinal stenosis, stroke, brain tumor, spinal anesthesia
Anxiety disorders	General anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder
Anesthesia	General or regional
Trauma (nonischemic)	Straddle injury, coital injury, pelvic trauma, intracavernous injection needle injury
Iatrogenic (nonischemic)	Penile revascularization surgery, intracavernous needle injury, shunt surgery

Hematologic disorders associated with ischemic priapism include sickle cell disease, glucose-6-phosphate deficiency, hereditary spherocytosis, and hematologic malignancies [13]. Sickle cell disease (SCD) deserves particular mention as it is a risk factor for major ischemic priapism and recurrent ischemic priapism, and is a major cause for emergency room visits [10]. A certain subset of SCD patients is at increased risk of priapism episodes due to polymorphisms in genes that regulate vascular tone, endothelial NO metabolism, coagulation, and cell hydration [14].

The longer an episode of ischemic priapism is left untreated, the greater the potential for long-term injury. Thus ischemic priapism is a medical emergency that requires urgent evaluation. Histopathologic studies demonstrate that irreversible corporal damage starts occurring around 4–6 h [15, 16]. At 24 h, the prolonged ischemia results in tissue necrosis, fibroblast proliferation, and fibrosis [12]. These changes ultimately can lead to erectile dysfunction, with significant social and psychological consequences [17].

Recurrent Ischemic Priapism

Recurrent ischemic priapism (RIP), also called stuttering priapism, is a form of ischemic priapism characterized by repeated episodes of ischemic priapism with intervening periods of detumescence [2]. This condition also has a variety of etiologies including neurologic disorders, sickle cell disease, and systemic illnesses predisposing patients to recurrent bouts of ischemic priapism. The natural history of RIP is heterogeneous with most episodes lasting less than 3 h and occurring during sleep, yet some may have major episodes occur on a regular basis [18, 19]. Indeed, approximately 30 % of patients experiencing RIP eventually progress to major priapism episodes [20]. Typically, these patients seek treatments to prevent future episodes.

Nonischemic Priapism

Nonischemic priapism, also known as high-flow or arterial, is a persistent erection in which unregulated cavernosal arterial inflow results in a persistent erection in the absence of sexual stimulation. It occurs in less than 5 % of priapism presentations [1, 2, 21]. This condition is usually not painful and the penis is not fully rigid. Its etiology is traditionally believed to be due to injury, trauma, or vascular malformations that result in alteration of the cavernous arterial blood supply. Fistula formation allows blood from the cavernous artery or other source to enter the lacunar spaces rather than the helicine arteries resulting in unregulated penile engorgement [22]. Other etiologies have also been reported with hematologic disorders and SCD where no clear history of or identifiable trauma or vascular malformation is noted [23]. The natural history of nonischemic priapism is one of spontaneous resolution with complications being rarely reported [2].

Workup and Evaluation

The diagnostic evaluation of priapism should be carried out promptly and expeditiously so therapeutic maneuvers may be instituted immediately if warranted. Priapism should be handled as a urologic emergency until the diagnostic evaluation is completed. The goal of the initial assessment lies in distinguishing between ischemic and nonischemic variants. Workup and evaluation should include a focused history, physical examination, and laboratory testing. Imaging may also be useful in evaluating and prescribing treatment regimens.

History and Physical Exam

History and physical examination will provide the majority of the diagnostic clues as to the etiology of the priapism. Key components of the history include onset, duration, presence of pain, pharmacotherapy, history of previous priapism episodes, prior surgeries or traumas, comorbid conditions (sickle cell disease or hematologic disorders), prior treatments, baseline erectile function, and alleviating maneuvers attempted. Physical examination should include close inspection of the genitalia, perineum, and abdomen [2]. The phallus is palpated and examined to assess for rigidity and tumescence, skin changes,

and tenderness. In nonischemic priapism, the corpora are typically tumescent but may not be completely rigid. Ischemic priapism exam findings classically include rigidity and tenderness of the cavernosal bodies with sparing of the glans. The groin should be inspected as well for signs of prior trauma, surgeries. A general exam may uncover signs of hematologic malignancy or chronic disease.

Laboratory Testing

American Urological Association (AUA) guidelines on priapism recommend blood gas analysis from corporal aspiration to confirm the diagnosis of ischemic priapism. Corporal blood is obtained using a large gauge (16 or 18 G) needle inserted directly into the corpus cavernosum mid-shaft and aspirated. To prevent equilibration with room air, the blood gas is immediately sent for analysis. This may be combined with therapeutic aspiration and/or irrigation efforts.

Typical findings on corporal blood gas analysis in the setting of ischemic priapism reveal: acidosis with a pH < 7.25, hypoxia with a $pO_2 < 30$ mmHg, and hypercarbia with a $pCO_2 > 60$ mmHg. In contrast, cavernous blood gases in men with nonischemic priapism are similar to the blood gases of arterial blood (pH 7.40, $pO_2 > 90$, $pCO_2 < 40$) [2].

Other serum laboratory testing may aid in determining the etiology of the priapism episode. A complete blood count can provide clues regarding acute infections or hematologic abnormalities, such as sickle cell, blood dyscrasias, or platelet abnormalities. Hemoglobin electrophoresis and reticulocyte count can further identify sickle cell disease or trait and other hemoglobinopathies [24]. Drug toxin screens through urine or blood can be helpful as psychoactive drugs (either legal or illegal) may cause priapism.

Imaging

Blood gas testing and color duplex ultrasonography are the most reliable methods of distinguishing ischemic and nonischemic priapism [12]. Penile imaging using color duplex ultrasonography can be valuable in diagnosing ischemic priapism in the emergent setting [25]. Color duplex ultrasonography presents a noninvasive alternative to cavernosal aspiration and may be utilized independently or to supplement the corporal blood-gas analysis findings when results are ambiguous [3]. Utilizing color duplex ultrasonography in the emergent setting does require that the operator is comfortable in the examination of the cavernosal arteries. Patients with ischemic priapism will have decreased or absent cavernosal arterial flow while nonischemic patients will demonstrate normal to high arterial flow velocities. Frog-leg or lithotomy positioning during ultrasonography allows for examination of the entire penile shaft in addition to the perineum. Such positioning allows for identification of anatomical malformations such as fistulae, straddle or scrotal injuries. Repeat ultrasonography can be useful to assess therapeutic response after interventions as overlying edema can sometimes make physical examination unreliable.

Penile arteriography can be helpful in select cases to identify the presence and localize an arteriolar-sinusoidal fistula in nonischemic priapism. This information can facilitate embolization, but is rarely used in an emergent setting. Color duplex ultrasonography has largely supplanted penile arteriography except in the setting of embolization [2].

Management

Ischemic Priapism

Ischemic priapism of longer than 4 h duration requires prompt medical attention and if untreated, has an increasing potential for injury over time. Diagnostic evaluation should be performed as expeditiously as possible and once the diagnosis of ischemic priapism is established, stepwise (least to more invasive) therapeutic maneuvers should be implemented. An outline of the management algorithm is demonstrated in Fig. 24.1. The objective of management is to correct the compartment syndrome, reestablish blood flow and relieve pain. Prior to

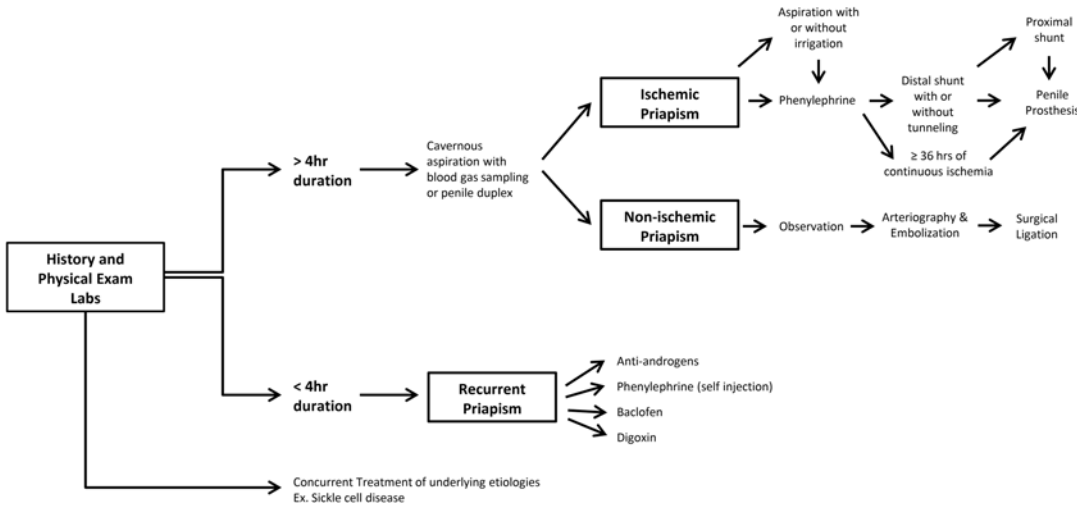

Fig. 24.1 Management algorithm for priapism

seeking medical attention, patients often report using maneuvers such as exercise ("steal syndrome"), warm or cold compresses, oral hydration, and ejaculation with widely varying levels of success [26]. Although there is no evidence-based recommendation regarding these methods, they can be used early on if historically successful and patients do not delay seeking timely medical attention.

During the acute episode, regardless of underlying disorder, the compartment syndrome must be addressed as expeditiously as possible with direct intracavernous treatment. Appropriate systemic treatment based on the etiology may be used concurrently, but should not be used solely to the exclusion of therapies directed at the penis [2]. Initial intervention should use therapeutic aspiration (with or without irrigation) and/or intracavernous injection of sympathomimetics. The aspirate may be sent for blood gas analysis. This can be combined with irrigation through the use of a three-way stopcock, allowing mechanical disruption of the consolidated clot. This approach aims to limit the ischemia from the compartment syndrome through decompression and restoration of blood flow to the corpora.

To increase the efficacy of resolution, injection of phenylephrine, a potent vasoactive selective alpha-1-adrenergic agonist (dosed 100–200 μg every 5 min until detumescence, with 1000 μg/h maximally) may be performed in combination with aspiration and irrigation [27, 28]. Resolution following sympathomimetic injection with aspiration has resolution rates of 43–81 %, compared to aspiration with or without irrigation alone (24–36 %) [2]. This process may be repeated several times prior to moving on to more invasive surgical interventions. Though several sympathomimetics have been used historically, phenylephrine is preferred due to its highly selective alpha-1-adrenergic activity with limited beta-adrenergic activity [8, 16, 29, 30]. Though risk of systemic side effects is minimal with intracavernous injection of phenylephrine, patients are routinely monitored with repeat blood pressure measurements and cardiac monitoring. Patients with a cardiac history or major cardiac risk factors may be more at risk for systemic side effects. Success and resolution is achieved when there is penile detumescence, pain is improved, and aspirate appears more consistent with freshly oxygenated blood. Adjunctive studies including penile ultrasound may be used for equivocal cases. The patient may need to be monitored and reexamined periodically for possible recurrent priapism or side effects from the treatment. Systemic therapies, if started, should be continued until the underlying etiology has been fully addressed. If the aspiration/irrigation maneuvers with or without sympathomimetics

fail, surgical options should be considered next. Though there is no clear consensus on when second-line options should be implemented and first-line treatments discontinued, clinical judgment should be employed to determine when first-line options are proving ineffective. Some advocate pursuing first-line options for at least 1 h before progressing to second-line therapies. Exceptions to this rule include continuous priapism episodes lasting greater than 72 h. Almost all studies indicate that prolonged ischemic damage of 72 h duration invariably results in erectile dysfunction, and first-line interventions have limited efficacy in this setting [1, 21, 31].

Recurrent Ischemic Priapism

Recurrent episodes of ischemic priapism can be due to a systemic disorder that predisposes the patient to recurrent episodes of prolonged penile ischemia, and a comprehensive evaluation should be conducted. Diagnosing the underlying etiology and instituting appropriate therapeutic interventions are key to preventing future episodes. In the acute setting of a major priapism episode, the primary management is similar to that of ischemic priapism management. If the etiology is known to be associated with a systemic illness, such as sickle cell disease, concurrent systemic therapies such as oxygen and exchange transfusions may be administered concurrently in the acute setting, but should not delay penile targeted therapies.

Preventative therapies are the main difference in the management of RIP. Insights into the pathophysiology of RIP in sickle cell disease suggest aberrations in NO signaling with down-regulation PDE5 as a primary mechanism underlying priapism. Low-dose PDE5 inhibitors (e.g., sildenafil 50 mg) taken daily and unassociated with sexual stimulation have demonstrated some benefit in reducing RIP episodes. The rationale for this approach is the restoration of NO balance with improved PDE5 function. Androgen inhibition is another approach used to prevent RIP episodes. Antiandrogens such as ketoconazole or trophic agents such as leuprolide acetate have been used in this context. They are contraindicated in younger patients though who have not achieved full sexual maturation and patients worried about their fertility. The evidence to support hormonal modulation is limited to small studies or case reports. Furthermore, these medications can have negative systemic side effects associated with androgen inhibition including gynecomastia, bone loss, and decreased libido. Self-injection is another option for RIP patients, whereby they self-inject phenylephrine after 1–2 h to terminate the erectile response before it becomes a major priapism episode.

Surgical Management of Ischemic Priapism

Surgical management of ischemic priapism has the same goals and objectives as the first-line therapies, notably to correct the compartment syndrome, reestablish blood flow, and relieve pain. Additionally, surgical management also offers additional options for patients where damage to cavernosa due to prolonged ischemia is too extensive and will result in permanent erectile dysfunction, such as early implantation of a penile prosthesis. These authors advocate a stepwise approach, with increasing invasiveness utilized, as sometimes the patient-reported history may be inaccurate.

Surgical management should be considered after first-line therapies fail, or if the clinical history and review of prior therapies suggest that surgical management should be offered initially. The International Society of Sexual Medicine (ISSM) recommends that penile shunting procedures be considered for priapism episodes lasting >72 h. Observation with supportive pain medication after failure of penile targeted therapy is an alternative to more invasive surgical therapies, but does not address the goals of relieving the compartment syndrome and reestablishing blood flow. Such an approach essentially allows the ischemia to run its course, which may take several days, and permanently damage the erectile mechanism, though some may argue that the damage has already been done at this time point.

There is generally some collateral blood flow to the superficial and bulbar arteries which makes necrosis of the entire penis uncommon. In general, the authors feel that surgical shunting maneuvers offer a good balance of benefits versus risk to make it worth attempting initially and allow more rapid resolution of the pain, if not sequelae from the compartment syndrome. All interventions should be accompanied by a well-documented discussion of the indications, risks, and benefits of the procedure and the high risk of permanent erectile dysfunction due to the natural history of this condition which increases with the duration of the priapism episode, irrespective of intervention. This discussion carries increased importance due to disproportionate amount of litigation in this area [1].

Shunting procedures treat ischemic priapism by establishing a communication between the sinusoids of the corpora cavernosal and the glans, corpus spongiosum or vein for drainage of blood [32]. The choice of shunting procedure is mainly dependent on the experience and familiarity of the provider with the technique. The distal shunts, corpora-glanular, are generally preferred because of the lower degree of technical difficulty and the low risk of complications [33].

Examples of distal shunts include: the Winter [34], the Ebbehoj [35], Al-Ghorab, the Burnett [33, 36], and the Lue T-shunt techniques [37]. These variants include percutaneous and open approaches. All serve to establish a window in the tunica of the corpora and create a controlled communication between the corpora and the spongiosum of the glans, allowing for an alternative path for egress of blood. The Burnett and Lue shunts also include cannulation, which involves the insertion of a dilator down the length of the corpora, which mechanically disrupts some of the consolidated clot, and allows for more efficient egress of blood. Distal shunts overall have high efficacy rates [12]. Although there are no head-to-head randomized trials comparing the various techniques, it is believed that the, Al-Ghorab, Burnett, and Lue may be more effective due to the larger window established between corpora and spongiosum, allowing for more efficient egress of blood [32].

Proximal shunts differ from distal shunts in that a window in the corpus cavernosum is made at the level of the crura and drainage is to the corpus spongiosum or a vein. The approach is usually transscrotal or transperineal. Examples include the Quackels (corporospongiosal) or Grayhack (corporosaphenous) shunt [38]. Though all shunting procedures carry risks of erectile dysfunction (ED), infection, fistula formation, stricture disease, urethral injury or cavernositis, the risk of complications is generally felt to be higher with proximal shunts [2]. Additionally, reported resolution rates have been lower though a large part of this is felt to be due to patient selection and time to treatment, as proximal shunts were typically reserved for cases in which distal shunts have failed.

Early penile prosthesis implantation is another surgical option selected based on the likelihood of permanent ED [39]. This assessment is based primarily on history and duration of the priapism episode as ischemic priapism episodes lasting continuously for >36 h almost universally result in permanent ED. Interventions that achieve partial restoration of blood flow but ultimately fail may alter the time frame, and thus, the ISSM recommends using 72 h from the initial event as a cutoff for strongly considering early penile prosthesis implantation. The advantages of such an approach are reduced fibrosis and maintenance of penile length. Prior shunting attempts are not a contraindication to early or delayed penile prosthesis implantation.

Nonischemic Priapism

Nonischemic priapism is not considered a urologic emergency, though the diagnostic evaluation should be carried out expeditiously to confirm this diagnosis. Given the different pathogenesis of this disease, with oxygenated arterial blood flowing to the corpora cavernosa in a high-flow fashion, the therapeutic maneuvers are also different. The spontaneous resolution rate of nonischemic priapism is as high as 62 %, and thus, patients can be observed in many cases and managed as outpatients [2]. Corporal

aspiration plays a primarily diagnostic role, and therapeutic aspiration/irrigation with sympathomimetics is not recommended by the AUA. Penile duplex of cavernosal arteries can also confirm this diagnosis. Given the high resolution rate, and non-emergent nature of this condition, initial management by observation is certainly reasonable and many urologists advocate this approach. Selective arterial embolization can be discussed and the risks and benefits weighed. Selective arterial embolization involves identification of the arterial fistulous formation and then the use of non-permanent or permanent materials to embolize and occlude the fistula. The AUA feels that absorbable, non-permanent materials are preferable to permanent materials as resolution rates are similar (74 % vs. 78 %), but carries a much lower erectile dysfunction rate (5 % vs. 39 %). Examples of absorbable materials include autologous clots and gelatin sponges. Surgical management consists of penile exploration and direct surgical ligation of the fistulae. It is felt to be an option of last resort as results appear inferior to that of embolization with efficacy rates of 63 % and ED rates of 50 % and higher risk of complications. Furthermore, the AUA recommends that surgery should be performed with the use of color duplex ultrasonography.

Conclusion

Most presentations of priapism will be that of ischemic priapism, and thus this condition should be treated as a medical emergency until a diagnostic evaluation has been carried out. Initial evaluation should focus on distinguishing between nonischemic and ischemic priapism. Once a diagnosis has been established a stepwise therapeutic plan should be implemented to relieve the compartment syndrome, reestablish blood flow and relieve pain. Increasingly invasive maneuvers may need to be employed and periodic reassessment should be instituted. Further work understanding the pathophysiology of this condition may allow better preventive options available to the practitioner.

References

1. Burnett AL, Bivalacqua TJ. Priapism: current principles and practice. Urol Clin North Am. 2007; 34(4):631–42. viii.
2. Montague DK, et al. American Urological Association guideline on the management of priapism. J Urol. 2003;170(4 Pt 1):1318–24.
3. Song PH, Moon KH. Priapism: current updates in clinical management. Korean J Urol. 2013;54(12):816–23.
4. Andersson KE, Wagner G. Physiology of penile erection. Physiol Rev. 1995;75(1):191–236.
5. Andersson KE. Pharmacology of penile erection. Pharmacol Rev. 2001;53(3):417–50.
6. Bivalacqua TJ, et al. New insights into the pathophysiology of sickle cell disease-associated priapism. J Sex Med. 2012;9(1):79–87.
7. Bivalacqua TJ, Burnett AL. Priapism: new concepts in the pathophysiology and new treatment strategies. Curr Urol Rep. 2006;7(6):497–502.
8. Anele UA, Morrison BF, Burnett AL. Molecular pathophysiology of priapism: emerging targets. Curr Drug Targets. 2015;16(5):474–83.
9. Corbin JD, Francis SH. Cyclic GMP phosphodiesterase-5: target of sildenafil. J Biol Chem. 1999;274(20):13729–32.
10. Broderick GA. Priapism and sickle-cell anemia: diagnosis and nonsurgical therapy. J Sex Med. 2012; 9(1):88–103.
11. Eland IA, et al. Incidence of priapism in the general population. Urology. 2001;57(5):970–2.
12. Salonia A, et al. European Association of Urology guidelines on priapism. Eur Urol. 2014;65(2):480–9.
13. Burnett AL, Bivalacqua TJ. Glucose-6-phosphate dehydrogenase deficiency: an etiology for idiopathic priapism? J Sex Med. 2008;5(1):237–40.
14. Elliott L, et al. Genetic polymorphisms associated with priapism in sickle cell disease. Br J Haematol. 2007;137(3):262–7.
15. Spycher MA, Hauri D. The ultrastructure of the erectile tissue in priapism. J Urol. 1986;135(1):142–7.
16. Kovac JR, et al. A pathophysiology-based approach to the management of early priapism. Asian J Androl. 2013;15(1):20–6.
17. Addis G, et al. The physical, social and psychological impact of priapism on adult males with sickle cell disorder. Chronic Illn. 2007;3(2):145–54.
18. Morrison BF, Burnett AL. Priapism in hematological and coagulative disorders: an update. Nat Rev Urol. 2011;8(4):223–30.
19. Morrison BF, Burnett AL. Stuttering priapism: insights into pathogenesis and management. Curr Urol Rep. 2012;13(4):268–76.
20. Emond AM, et al. Priapism and impotence in homozygous sickle cell disease. Arch Intern Med. 1980;140(11):1434–7.
21. Burnett AL, Sharlip ID. Standard operating procedures for priapism. J Sex Med. 2013;10(1):180–94.

22. Yuan J, et al. Insights of priapism mechanism and rationale treatment for recurrent priapism. Asian J Androl. 2008;10(1):88–101.
23. Melman A, Serels S. Priapism. Int J Impot Res. 2000;12 Suppl 4:S133–9.
24. Kato GJ. Priapism in sickle-cell disease: a hematologist's perspective. J Sex Med. 2012;9(1):70–8.
25. LeRoy TJ, Broderick GA. Doppler blood flow analysis of erectile function: who, when, and how. Urol Clin North Am. 2011;38(2):147–54.
26. Adeyoju AB, et al. Priapism in sickle-cell disease; incidence, risk factors and complications – an international multicentre study. BJU Int. 2002;90(9):898–902.
27. Muneer A, et al. Investigating the effects of high-dose phenylephrine in the management of prolonged ischaemic priapism. J Sex Med. 2008;5(9):2152–9.
28. Munarriz R, et al. Management of ischemic priapism with high-dose intracavernosal phenylephrine: from bench to bedside. J Sex Med. 2006;3(5):918–22.
29. Bodne DR, et al. The application of intracavernous injection of vasoactive medications for erection in men with spinal cord injury. J Urol. 1987;138(2):310–1.
30. Lee M, Cannon B, Sharifi R. Chart for preparation of dilutions of alpha-adrenergic agonists for intracavernous use in treatment of priapism. J Urol. 1995;153(4):1182–3.
31. Burnett AL. Surgical management of ischemic priapism. J Sex Med. 2012;9(1):114–20.
32. Brant WO, et al. T-Shaped shunt and intracavernous tunneling for prolonged ischemic priapism. J Urol. 2009;181(4):1699–705.
33. Burnett AL, Pierorazio PM. Corporal "snake" maneuver: corporoglanular shunt surgical modification for ischemic priapism. J Sex Med. 2009;6(4):1171–6.
34. Winter CC. Cure of idiopathic priapism: new procedure for creating fistula between glans penis and corpora cavernosa. Urology. 1976;8(4):389–91.
35. Ebbehoj J. A new operation for priapism. Scand J Plast Reconstr Surg. 1974;8(3):241–2.
36. Segal RL, et al. Corporal Burnett "Snake" surgical maneuver for the treatment of ischemic priapism: long-term followup. J Urol. 2013;189(3):1025–9.
37. Lue TF, Pescatori ES. Distal cavernosum-glans shunts for ischemic priapism. J Sex Med. 2006; 3(4):749–52.
38. Quackels R. Treatment of a case of priapism by cavernospongious anastomosis. Acta Urol Belg. 1964; 32:5–13.
39. Ralph DJ, et al. The immediate insertion of a penile prosthesis for acute ischaemic priapism. Eur Urol. 2009;56(6):1033–8.

Ejaculatory Disorders

25

Michael J. Butcher and Robert E. Brannigan

Introduction

The normal male sexual cycle consists of four stages: desire, arousal, orgasm, and resolution. As Masters and Johnson originally reported, each of these stages is associated with distinct physiological changes in the male [1]. Ejaculation, which normally occurs during the orgasm phase, is a highly complex, integrated process essential for the normal delivery of semen into the female reproductive tract during intercourse. Ejaculation disorders can lead to impaired reproductive potential in men and may necessitate the use of a variety of advanced diagnostic and therapeutic maneuvers. The impact of ejaculatory dysfunction is not confined to detrimental effects on men trying to achieve a pregnancy, as a recent study by Rosen et al. showed [2]. In a survey of 12,815 US and European men aged 50 years or older, the authors found that ejaculatory disorders are common, affecting 30.1 % of men between 50 and 59 years of age. A majority (50.2 %) of these affected men reported bother due to their ejaculatory problems. The authors noted that despite the pervasive focus among many clinicians on erectile dysfunction when assessing a patient's sexual health, ejaculatory problems are almost as common and should also be considered. For these reasons, physicians should be capable of identifying and treating the broad spectrum of ejaculatory disorders; this is essential in order to effectively care for the large numbers of affected men.

The Physiology of Ejaculation

Ejaculation in human men occurs simultaneously with orgasm. The concurrent timing of ejaculation with the rewarding sensory experience of orgasm, from an evolutionary perspective, serves to facilitate sexual behavior and human reproduction [3]. Despite the close temporal link between orgasm and ejaculation, these are two distinct and unique physiologic events. Orgasm is largely a central nervous system process that can be generated by cerebral stimulation without any accompanying genital input [4]. Thus, it is possible for men to experience orgasm in the absence of ejaculation. Clinically, this is illustrated in men who have undergone radical retropubic prostatectomy, with surgical extraction of

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their ampullary vas deferens, seminal vesicles, and prostate gland. Despite the absence of these accessory sex glands that play a central role in ejaculation, patients who have undergone radical prostatectomy are typically capable of achieving orgasm postoperatively [5].

Ejaculation consists of two phases: emission and expulsion. Each phase is coordinated by anatomical structures functioning together in a highly integrated fashion and is separately discussed below.

Emission Phase

The anatomical structures involved in emission include the epididymis, vas deferens, seminal vesicles, prostate gland, prostatic portion of the urethra, and bladder neck. These structures have both sympathetic and parasympathetic innervation with nerve fibers that arise predominately from the pelvic plexus. These nerve fibers are located in the retroperitoneum, traveling alongside the rectum and also lying posterolateral to the seminal vesicles [6]. Pelvic plexus nerve fibers come superiorly from the hypogastric and pelvic nerves, and inferiorly from the caudal paravertebral sympathetic chain [7]. Emission is initiated when afferent stimulatory input, primarily arising from sensory fibers within the glans penis, is integrated at the level of the spinal cord [8]. Sympathetic nerves (T10-L2) mediate the release of several neurotransmitters, including norepinephrine, causing epithelial cell secretion and smooth muscle cell contraction throughout the excurrent ductal system [9]. As a result, accessory gland secretions are admixed with spermatozoa and ejected into the posterior urethra.

Expulsion Phase

The anatomical structures involved in seminal expulsion include the bladder neck, urethra, and striated pelvic muscles. Expulsion is a spinal cord reflex triggered once inevitability, or "the point of no return," is reached during sexual activity. During expulsion, the bladder neck smooth muscle fibers, under sympathetic fiber stimulation, forcibly contact to prevent retrograde ejaculation. Next, the striated pelvic floor muscles, in particular the ischiocavernosus and bulbocavernosus muscles, contract in an intermittent, rhythmic fashion, and the external urethral sphincter relaxes. While these muscles are innervated solely by the somatic nervous system (S2–4), the expulsion phase of ejaculation does not appear to have any component of volitional control. In the setting of tight bladder neck contraction, the series of striated pelvic muscular contractions leads to antegrade propulsion of semen through the prostatic, bulbar, and penile urethra and out the urethral meatus. To date, the specific trigger for the expulsion phase has not been clearly elucidated. Early work in a rat model suggested that the presence of semen in the bulbous urethra is the predominant factor that triggers seminal expulsion [10]. Subsequent works describe the presence of a spinal ejaculatory generator that leads to the expulsion of seminal fluid once a critical level of spinal activation has been achieved [11]. The spinal ejaculatory center is believed to integrate stimuli from peripheral and central sites, with efferent output through both parasympathetic and somatic pathways [12]. In 2002, Truitt and Coolen reported that neurons having a role in generating ejaculation are located within lamina X and the medial portion of lamina VII of lumbar segments 3 and 4. These neurons receive descending input from the nucleus paragigantocellularis, the medial preoptic area, and the paraventricular nucleus of the hypothalamus, each providing supraspinal modulatory effects on the spinal ejaculatory generator [13]. While descending cortical input may influence ejaculation, it is not essential for ejaculation to occur. Men with complete spinal cord transection superior to the tenth thoracic segmental level (superior to the location of the spinal ejaculatory generator) exemplify this point; in these men, the ejaculatory reflex is typically still feasible. Penile vibratory stimulation is routinely used in such patients to induce the ejaculatory response for reproductive purposes, in order to collect sperm for assisted reproductive tech-

niques, such as intrauterine insemination or in vitro fertilization. The intact function of the spinal ejaculatory generator neurons is essential for normal ejaculatory function, as their ablation leads to the complete loss of ejaculatory function [12].

Premature Ejaculation

Premature ejaculation (PE) is a highly prevalent condition; based on data from the National Health and Social Life Survey, this condition affects 21 % of men between 18 and 59 years of age in the USA [14]. This disorder is classified into two categories: primary PE, which is present from the time a male first becomes sexually active and secondary PE, which is acquired later in life.

Etiology

The specific cause of PE is not known. A number of etiologies have been proposed, including a variety of psychological and organic causes. Dunn and colleagues performed a cross-sectional population survey in 1999 and found that anxiety was strongly associated with the presence of PE. While the authors acknowledge that the direction of this and other associations from their study need to be clarified, their results suggest that psychological factors such as anxiety could possibly have a causative role in sexual problems such as PE [15]. In contrast to psychosexual causes, organic causes have also been postulated to cause PE. Waldinger et al. proposed that PE is a neurobiological disorder due to serotonergic hypoactivity.

Studies of male rats have shown that serotonin (5-hydroxytryptamine or 5-HT), and various serotonin receptors, play a role in the process of ejaculation [3]. Activation of 5-HT_{1B} and 5-HT_{2c} receptors delays ejaculation, while activation of 5-HT_{1a} receptors facilitates ejaculation. Some authors have related decreased central serotonergic activity (increased 5-HT_{1a} sensitivity or decreased 5-HT_{2c} sensitivity) to PE.

Diagnosis

One of the first definitions for PE was offered by Masters and Johnson, who described it as the inability of the male partner to delay ejaculation long enough for the female partner to achieve orgasm 50 % of the time [16]. Since that time, the definition has evolved. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the American Psychiatric Association's classification and diagnostic document. While the DSM-5 was published in May 2013, the DSM-IV-revised version 4 (DSM-IV-TR) was the document used as a reference in many of the seminal studies regarding PE. The DSM-IV-TR highlights the individual and interpersonal distress caused by male climax earlier than desired by the male. The key aspects of the DSM-IV-TR definition include:

1. Reduced control over ejaculation.
2. A decrease in the patient's and/or partner's satisfaction with sexual intercourse.
3. Distress or bother in the patient and/or partner regarding the PE.

This DSM-IV-TR definition has been widely utilized clinically, and the Premature Ejaculation Diagnostic Tool (PEDT) is a five-item questionnaire developed specifically to apply the DSM-IV-TR criteria for PE. In 2006, Waldinger and Schweitzer reported on the limitations of the DSM-IV criteria for PE diagnosis, noting that it resulted in a low, positive predictive value [17]. Symonds et al. subsequently published an article arguing the opposite, stating the PEDT is a reliable and valid PE diagnostic tool [18].

Many investigators favor the use of intravaginal ejaculation latency time (IELT) to diagnose PE. IELT is defined as the time from vaginal intromission to the onset of ejaculation [19]. Advantages include that IELT is, at least in theory, a reproducible, objective measure. However, a 2005 article by Patrick et al. highlighted some of the limitations of IELT [20]. The authors assessed 207 men with PE and 1380 men without PE. At the time of the first study visit, subjects were asked to estimate their own IELT. After this visit, the patient and his

partner were provided with a stopwatch and journal in which to document each episode of sexual intercourse. The IELT was measured and recorded by the female partner. For men with PE, the median measured IELT was 1.8 min, while the mean estimated value was 2.0 min. For men without PE, the median measured IELT was 7.3 min, while the mean estimated IELT was 9.0 min. This study highlights the fact that men with and without PE tend to overestimate their IELT, and it also sheds light on the time of ejaculation in both normal men and men diagnosed with PE [20]. While no firm IELT defining PE has been determined, some authors consider an IELT < 2 min as characteristic of PE.

Normative IELT data have been provided by a recent multinational, community-based, age-ranging study using IELT assessed by stopwatch [21]. The authors found that IELT decreased with age and varied among countries. The distribution of IELT was positively skewed, with a median value of 5.4 min (0.55–44.1 min). Waldinger et al. suggested that men with an IELT < 1 min (0.5 percentile of subjects) have "definite" PE, while men with IELT's 1–1.5 min (0.5–2.5 percentile of subjects) have "probable" PE [22].

The Sexual Assessment Monitor is a new device developed by Dinsmore and colleagues to measure the time from the start of vibration to ejaculation. This device has been shown as safe and effective, and has been validated to collect IELT data in both healthy volunteers and men with PE [23].

In 2003, the Second International Consultation on Sexual Dysfunction (ICSD) met to develop evidence-based guidelines for a variety of disorders of sexual function. At this meeting, PE was defined based on three criteria:

1. Brief ejaculatory latency.
2. Loss of control over ejaculation.
3. Psychological distress to the patient and/or his partner [24].

The specific definition of PE generated at this meeting was, "ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother and distress and over which the sufferer has little or no voluntary control [25]." While the ICSD noted that men with IELT < 2 min qualify as having PE, they stipulated that diagnostic criteria required all three components: decreased IELT, inability to delay/control ejaculation, and marked associated distress over their condition. The Fourth International Consultation on Sexual Medicine will be held in June, 2015 in Madrid, Spain and will be hosted by the International Society of Sexual Medicine.

In 2004, the American Urological Association published "AUA Guideline on the Pharmacologic Management of Premature Ejaculation" [26]. This document was reviewed and the validity confirmed by the AUA in 2010. The panel members conducted a literature review and found a lack of standardization in PE studies, with a wide variety of PE definitions, study criteria, and physiological measurements. The panel determined that a meta-analysis was thus inappropriate, particularly in consideration of the variety of PE outcomes measures and populations studied. The panel's recommendations were thus developed based on consensus combined with a review of the limited evidence available.

The guidelines' first recommendation states, "The diagnosis of PE is based on sexual history alone. A detailed sexual history should be obtained from all patients with ejaculatory complaints." The authors highlighted the importance of eliciting a number of clinical factors from the patient, including the frequency and duration of PE, the degree of stimulation resulting in PE, the impact of PE on sexual activity, factors that exacerbate or alleviate PE, and the frequency and nature of sexual activity. The guidelines stipulate that special laboratory or physiological testing is *not* indicated unless the history or physical exam reveals the presence of other complicating medical factors in need of additional investigation.

Treatment

Therapies for PE include psychological, behavioral, and pharmacological approaches. In general, men with lifelong PE likely have lower ejaculatory thresholds compared to unaffected men, and thus may benefit most from medical

therapies [27, 28]. In contrast, men with a history of acquired PE are more likely to be better treated with cognitive or behavioral therapy [29]. Among the psychological approaches, psychotherapy has been reported as a primary therapy, but there is a lack of well-designed clinical trials assessing the efficacy of this intervention.

Behavioral Techniques

Behavioral techniques include the "stop and start technique" and the "squeeze technique." With the "stop and start technique," patients are instructed to manually stimulate themselves in a controlled fashion and involve their partner in the manual stimulation once controlled arousal has been achieved. The couple then proceeds on to intercourse [16]. The "squeeze technique" is very similar to the "stop and start technique," except the penis is manually squeezed during the times when stimulation is stopped [30]. The obvious advantage of behavioral techniques is that they are nonpharmacologic and thus avoid possible side effects associated with medical therapies. While some authors report success with behavioral approaches, these treatment modalities are overall poorly studied and lack long-term efficacy [31].

Pharmacological Therapies

A number of pharmacological therapies have been utilized to lengthen IELT for men with PE. These therapies include both topical and oral agents, and dosing varies from on-demand to daily schedules.

The ICSD recognized three pharmacologic treatment options for PE:

1. Topical anesthetics (lidocaine or prilocaine).
2. Daily treatment with serotonergic antidepressants (paroxetine 20–40 mg, sertraline 50–100 mg, fluoxetine 20–40 mg, or clomipramine 10–50 mg).
3. On-demand treatment with antidepressants.

The ICSD Guidelines stated that none of the above drugs have been approved for the treatment of PE by regulatory agencies, and the majority of studies to assess their efficacy are limited by inadequate design (As discussed elsewhere in this book, dapexetine was subsequently approved for use in Europe.).

Topical Therapies

Topical therapies address the issue of "penile hypersensitivity." Local anesthetic medications are available in topical gel, cream, or spray forms. Busato et al. conducted a double-blind, randomized, placebo-controlled study assessing topical lidocaine–prilocaine; they reported a significant increase in IELT from 1.49 to 8.45 min in the treatment group versus 1.67–1.95 min in the placebo group [32]. In this particular study, no systemic side effects were reported. Possible side effects do include skin irritation or numbness and erectile dysfunction [33]. Additionally, transfer of these topical medications from the treated male to his partner is another possible bothersome side effect potentially limiting the use of this mode of therapy. Hence, the ICSD noted that while topical therapy is moderately effective, penile hypoesthesia is a significant adverse side effect in the male. In the female, transvaginal absorption with possible vaginal numbness and female anorgasmia may limit efficacy for the couple if a condom is not used.

Oral Therapies

A number of oral therapies are used to treat PE. This includes the phosphodiesterase type 5 (PDE-5) inhibitors, as well as the selective serotonin reuptake inhibitor (SSRI) agents. Neither of these classes of drug was developed specifically for the treatment of PE, and the use of these medications for patients with PE is thus done in an off-label fashion. However, the AUA Guideline on the Management of Ejaculatory Dysfunction recommends, "In patients with concomitant PE and ED, the ED should be treated first." The rationale for this approach is that PE sometimes improves concomitantly with improvement in the ED. The authors note that in this setting the intense stimulation needed to achieve and maintain an erection, or the anxiety associated with ED, may cause secondary PE.

PDE-5 Inhibitors

The use of PDE-5 inhibitors has been found to provide limited efficacy for the treatment of PE in men without concurrent ED. Nitric oxide (NO), which is augmented by the use of PDE-5 inhibitors, exerts both central and peripheral effects on emission. Hull et al. reported that systemic administration of a nitric oxide synthase inhibitor (*N*-nitro-L-arginine-methyl ester) led to a decrease in latency to the first emission and increased the overall number of emissions [34].

These same authors reported that NO causes a decrease in peripheral smooth muscle activity, likely mediated by a decrease in sympathetic nervous system activity, thus leading to inhibited seminal emission. They concluded, based on their collective findings, that NO may help prevent PE.

The PDE-5 inhibitors have been evaluated clinically in numerous studies for the treatment of PE, both as monotherapy and also in combination with SSRI agents. In 2005, McMahon et al. reported the results of an 8-week, double-blind, placebo-controlled, parallel group study of sildenafil citrate in men aged 18–65 years with PE [35]. The authors reported that while IELT was not significantly improved, subjects on sildenafil did report increased confidence, increased the perception of ejaculatory control, increased overall sexual satisfaction, and decreased refractory time to achieve a second erection. The authors suggested that the lack of a significant increase in IELT suggests a lack of direct central or peripheral effect of sildenafil on ejaculation function. They also noted that the perceived improvement in ejaculatory control and confidence may have been related to the improved erectile functioning and reduced performance anxiety.

McMahon et al. subsequently published a systematic review of the efficacy of PDE-5 inhibitors in the treatment of PE in 2005 [35]. They found that 13 of the 14 published studies did not fulfill evidence-based medicine criteria for ideal PE drug trial design (double-blind, placebo-controlled study, differentiation of lifelong and acquired PE subgroups, exclusion or categorization as a separate subgroup men with concurrent ED or other sexual disorders, and consistent and objective physiological measurements or use of sensitive, validated outcome assessment instruments as study endpoints). The one study that did fulfill these ideal design criteria reported that the treatment with sildenafil failed to increase baseline IELT in men with PE. The authors concluded that there is no convincing evidence to support any role for the use of PDE-5 inhibitors in men with lifelong PE and normal erectile function. They did, however, acknowledge that there is limited evidence for the role of PDE-5 inhibitors either alone or in combination with on-demand or daily SSRI agents for men with PE *and* concurrent ED. They proposed that the mechanisms of action in these men include: the ability to maintain an erection after ejaculation, reduction of the erectile refractory period with reliance on a second, subsequent erection which may be better controlled, reduction in performance anxiety with resultant better erections, and/or a decrease in erectile threshold to a diminished level of arousal, facilitating a relatively greater level of arousal to achieve ejaculation threshold.

Selective Serotonin Reuptake Inhibitor (SSRI) Agents

The SSRI class of medications has been used widely to treat PE. Serotonin is active in the nerve synapse, and low levels are known to cause depression. The tricyclic antidepressant (TCA) and SSRI agents were developed for the treatment of depression. While the TCA agents prevent the reuptake of both serotonin and norepinephrine, the SSRI agents are more specific and work by inhibiting the reuptake of serotonin into the presynaptic nerve terminal. These agents thus prolong or promote serotonin's effects. Therefore, it is not surprising that many patients who were administered SSRI agents, which were developed for the treatment of depression, complained of increased time to reach ejaculation on this therapy.

The ICSD reported that daily paroxetine provides the most robust delay in ejaculation, and delay with daily use of any of these agents is noted by the second week of therapy. Regarding efficacy of on-demand therapy with antidepressants, the ICSD was unable to provide

conclusions due to the limited number of studies, insufficient number of patients, and inadequate study designs.

At the time of the publication of the AUA Guideline on the Pharmacological Management of PE document, as well as at this time, there is no pharmacological agent approved by the US Food and Drug Administration (FDA) for the treatment of PE. As is stated in the AUA Guideline, PE can be treated successfully with several different SSRI agents. The off-label use of the SSRI agents, fluoxetine, paroxetine, sertraline, and the TCA agent clomipramine, were noted in the Guideline to have demonstrated enhanced benefit over placebo in the treatment of PE. Other agents, such as nefazodone, citalopram, and fluvoxamine, were reported to be ineffective in treating PE.

The AUA panel charged with developing the Guideline could not conclude whether daily dosing or on-demand dosing was superior. The authors also noted that medical therapy only provides symptomatic relief, and not cure of PE. Adverse events are a potential concern when using antidepressant pharmacological agents. While adverse event profiles have not been widely studied in the setting of PE therapy, those associated with the use of SSRIs and TCA agents in patients with depression include: dry mouth, drowsiness, nausea, and decreased libido. The most concerning adverse event is called "serotonergic syndrome." In mild cases, patients experience headache, dizziness, sweating, and nausea, while in severe cases patients may experience delirium, hyperthermia, and rigidity. Generally, the dosages of these medications used in treating men with PE are lower than dosages used to treat depression; nonetheless, these potential adverse events remain a concern and should be discussed with patients prior to initiating therapy.

Special mention should be made of dapoxetine hydrochloride, another SSRI agent. Dapoxetine hydrochloride, a short acting SSRI is being studied for the specific indication for PE. In 2006, Pryor et al. published an article in *Lancet* summarizing the efficacy of dapoxetine in two identically designed 12-week, randomized, double-blind, placebo-controlled Phase III clinical trials [36]. Both studies evaluated men with moderate to severe PE who received placebo, dapoxetine 30 mg, or dapoxetine 60 mg as needed 1–3 h prior to intercourse. Both dosages of dapoxetine resulted in prolonged IELT when compared to placebo ($p=0.0001$), and both dosages were associated with only mild side effects [36]. Safarinejad published the results of a double-blind, placebo-controlled, fixed-dose, randomized study of dapoxetine in the treatment of PE in 2007 [37]. He reported that daily dapoxetine has moderately better results in terms of IELT and intercourse satisfaction when compared to placebo. Dapoxetine did not provide men with long-term benefit after withdrawn. In November 2005, the FDA denied the application of dapoxetine in the treatment of PE [38]. However, in January 2012, the European Medicines Agency Committee for Medicinal Products for Human Use authorized the marketing of dapoxetine in the member states of the European Union. An article by Waldinger et al. in the *Journal of Sexual Medicine* questioned what the authors termed the "statistically significant but clinically small ejaculation-delaying effects of dapoxetine" [38]. The authors also questioned several aspects of the methodology of the Phase III clinical trials, including the importance of patient reported outcomes of perceived control over ejaculation and satisfaction with sexual intercourse, over more objective measures such as IELT.

In summary, both the AUA and ICSD guidelines recommend specific antidepressants and topical anesthetics for the pharmacologic management of PE. Only the ICSD, however, highlights the benefits of psychological and behavioral interventions.

Miscellaneous Approaches

In closing, some investigators have reported efforts to block nerve receptors for penile tactile stimuli via selective dorsal penile nerve division and hyaluronic acid gel injection. Both of these approaches have been reported to prolong IELT, but clearly need further investigation given their very limited evaluation to date [39].

Delayed Ejaculation (Inhibited Ejaculation and Anejaculation)

Delayed ejaculation (DE) is a poorly understood disorder of ejaculation with complex etiologies and multiple treatment options. There is a paucity of randomized, placebo-controlled, blinded research on the topic with only consensus and expert opinions on treatment exist. This section of the chapter discusses etiology, diagnosis, and treatment associated with DE.

Terminology

DE can be defined as personal distress caused by the persistent or recurrent delay, difficulty or absence of orgasm after sufficient sexual stimulation [40]. A similar definition also added the caveat that the DE cannot be attributed to general medical conditions, drugs, medications, or other axis I disorders [41]. There are five axes of psychiatric evaluations that identify different aspects of disorders and disability attributed to a diagnosis in DSM-IV-TR. Axis I—all psychological diagnosis; Axis II—personality disorders and mental retardation; Axis III—general medical conditions and physical disorders; Axis IV—psychosocial and associated environmental factors; Axis V—a global assessment of function. DE thus, is a medical and/or psychological condition that is not associated with other types of psychiatric diagnosis (i.e., paraphilias, psychotic disorders, etc.).

There are no commonly accepted standard times to define delayed ejaculation. Median intravaginal ejaculation latency time (IELT) is 5.4 min in normal subjects from around the world with a range of 4–10 min following intromission [20]. Men who report distress or cease sexual activity due to fatigue or irritation after two standard deviations of the mean IELT (21–23 min) would be considered pathologic [42].

Primary DE is also known as congenital DE, global DE, or lifelong DE which occurs from the first sexual experience through their lives. Anejaculation (absence of the ejaculation reflex) and aspermia (lack of release of an antegrade ejaculate) often accompany primary DE. Secondary DE or, acquired DE is intermittent or situational being restricted to different forms of stimulation resulting in ejaculation, usually outside of partnered sex. An example of secondary DE would be the ability to have an ejaculation with masturbation or oral sex but not with coitus.

Retrograde ejaculation is the expulsion of semen backward into the bladder rather than forward and out through the urethral meatus. Retrograde ejaculation can be caused by an, incompetent bladder neck, a history of prior bladder neck surgery such as TURP or medications such an alpha antagonists. In retrograde ejaculation an orgasm commonly occurs and the intravaginal orgasmic time is not disrupted. Antegrade ejaculation is the normal, forward propulsion of semen. Aspermia is defined as the absence of an antegrade ejaculate, which can cause fertility problems but is not necessarily accompanied by anorgasmia. Likewise, a decrease in ejaculate volume with satisfactory timing of ejaculation is not considered DE and may be reflective of retrograde ejaculation.

Epidemiology

DE is a rare condition. The true incidence and prevalence of DE is likely underreported due to its varied etiologies and incomplete sexual histories obtained by practitioners as well as the disparate non-standardized terms used to describe the entity as demonstrated above. Primary anorgasmia was found in 15 per 10,000 in 1948 [43]. Delayed ejaculation occurred in 2–11 % in the general heterosexual population, and upward of 20–39 % in homosexual and HIV-infected males [44–47]. A 2003 London study found an incidence of 2.5 % of the male general population were unable to have an ejaculation ≥75 % of the time [48]. An American sexual dysfunction national health survey that included 1410 men found that 8 % felt they had been unable to have a climax or ejaculation for a 2 month period over 1 year [14]. Men are living longer and are taking more medications that can potentially affect ejaculation. The recalcitrant nature of DE likely

results in underreporting. This condition also suffers from a lack of understanding and a paucity of quality treatments.

Clinical Impact

The impact of DE on men can be quite detrimental. A cross-sectional study of 331 heterosexual men aged 18–65 found that men with DE had additional medical and sexual problems (hypertension, diabetes, obesity, hyperlipidemia, tobacco use, mood disorders, alcohol abuse, etc.) [49]. Medical conditions predicted scores on both DE and low libido. In addition, performance anxiety was associated with DE. It was not clear whether DE resulted from stress in home/work life or vice versa, but we know that psychological stress has been shown to cause DE [14]. Sexual dissatisfaction, anxiety, depression, performance anxiety, relationship distress, shame, low self-image, intimacy avoidance, and relationship dissatisfaction all can be associated with DE [16, 50–54]. Relationship quality and level of intimacy are key factors in the sexual experience that can bring support, happiness, and satisfaction. DE impacts the patient and the partner necessitating cooperation of both in the treatment for mutually satisfying sexual experiences.

Etiology

DE is a complex medical condition with a multitude of etiologies. Genetically predetermined ejaculatory thresholds in combination with psychosocial, biologic, behavioral, and cultural influences contribute to DE [55–57]. Age, congenital, anatomic, neurogenic, infection/inflammation, endocrine, pharmacologic, and psychological issues all play a causative role in DE development (Table 25.1).

Age

Age causes progressive atrophy of sexual organs, decreased testosterone production, and decreased intensity of orgasm [58]. Neurogenic pathologies that compromise the nervous system and signal transduction may be responsible for this aging effect. The fast conduction within the peripheral nervous system progressively deteriorates in the third decade of life [46]. Difficulty achieving the sensory threshold needed for ejaculation stems from myelin collagen infiltrates, dermal atrophy, and degeneration of Pacinian corpuscles which are sensory units within the dermis [59, 60]. As a result, IELT typically increases in older men [61].

Older patients have more comorbid diseases that contribute to DE. Some commonly seen disease states include depression, peripheral vascular disease, diabetes, and psychiatric pathology. Lifestyle factors such as smoking, obesity, alcohol use, inactivity, and loneliness (such as loss of a partner) can be potent inhibitors of ejaculation and overall sexual function and satisfaction [62, 63].

Congenital

The three most common congenital abnormalities that may affect ejaculation are Wolffian duct abnormalities, Mullerian duct cysts, and prune belly syndrome. Mullerian duct cysts are caused by persistence of embryonic paramesonephric ducts that form a cystic structure within the prostate that can cause obstruction and decreased ejaculate.

Genetic disorders can also cause an absence of structures like the vas deferens or seminal vesicles in carriers of cystic fibrosis (CFTR) gene. Wolffian duct abnormalities can lead to missing or abnormal components of the genital tract, including the bladder neck and ejaculatory ducts. Those born with imperforate anus who have undergone repair were found to have ejaculatory failure which often attributed to nerve damage from surgery [46]. In prune belly syndrome, ejaculation and emission problems occur in part from prostatic hypotrophy and bladder neck disorders. Retrograde ejaculation and climacturia (ejaculation with urine leak with orgasm) have been described [40].

Anatomic/Trauma

Surgical procedures are performed on many men to treat certain disease states in the pelvis that can affect the genital tract. Treatments such as transurethral resection of the prostate and transurethral incision of the bladder neck/

Table 25.1 Etiologies of anorgasmia, anejaculation, and delayed ejaculation

Aging male psychogenic	Degeneration of penile afferent nerves inhibited ejaculation
Congenital	Genetic abnormalities Mullerian duct cyst Wolffian duct abnormalities Prune Belly syndrome Imperforate anus
Anatomic causes	Bladder neck reconstructive surgery Transurethral resection of prostate Bladder neck incision
Neurogenic causes	Diabetic autonomic neuropathy Multiple sclerosis Spinal cord injury Radical prostatectomy Proctocolectomy Bilateral sympathectomy Abdominal aortic aneurysmectomy Para-aortic lymphadenectomy
Infective/inflammation	Urethritis Orchitis Prostatitis Genitourinary tuberculosis Schistosomiasis
Endocrine	Prolactin disorders Hypogonadism Hypothyroidism Hyperthyroidism
Medication	See additional table
Psychological	Acute psychological distress Relationship distress Psychosexual skill deficit Disconnect between arousal and sexual situations Masturbation style

Data from refs. [40, 46, 50, 52, 123]

prostrate can cause retrograde ejaculation and DE. A post-ejaculatory urinalysis is needed to distinguish between the two conditions. Radical prostatectomy for cancer results in removal of the prostate gland and seminal vesicles, and as a result no antegrade ejaculation will occur. Other deep pelvic surgeries such as cystectomies and perineal resections can affect sexual functions through disruption of pelvic ganglia. Retroperitoneal lymph node dissection can result in problems in emission from disruption of the sympathetic chain.

Neurogenic

Neurogenic causes of DE can be divided into medical disease states and trauma. Diabetes and multiple sclerosis are strongly associated with DE [50, 64, 65]. DE and problems with emission and ejaculation occur in up to 33 % of diabetic men [52]. A survey of male patients with multiple sclerosis demonstrated up to 45 % being affected by DE [66].

Ninety-five percent of men with complete upper motor neuron lesions are not able to ejaculate [67]. The ability to ejaculate increases progressively with descending spinal injuries. Ejaculatory dysfunction can occur with damage to the sympathetic ganglia resulting from para-aortic lymphadenectomy. Sperm banking should be discussed with young men who will undergo this procedure as seminal emission can be completely disrupted rendering post ejaculatory urine processing impossible [40]. Prostate surgery, pelvic surgeries and even radiation to these areas can affect the nervous system responsible for ejaculation as well as erections.

Men who have primary DE may also have a degree of hyposensitivity to the glans penis and overall decreased excitability perhaps secondary to decreased nerve density and/or deposition in sexual organs. Men with primary DE often have greater success ejaculating with masturbation than with partnered sex [68]. This is different than men with PE who typically have greater success (increased IELT) with partnered sex [40].

Infective/Inflammation

Orchitis, epididymitis, and severe prostatitis can all lead to DE when pain leads to subsequent fear of pain with ejaculation. Urethritis, epididymitis, tuberculosis of the genitourinary tract, and schistosomiasis can all cause obstruction and cicatrization or scarring of the ejaculatory ducts. This can present as hematospermia, which usually is benign. However, 8 % of men under 30 years old with hematopsermia were found to have other serious conditions present in an international study [69]. When investigating ejaculatory pain with transrectal ultrasound, calcifications from

tuberculosis or other etiologies including idiopathic causes can be identified. Often prostatic, seminal vesicle, and ejaculatory duct stones can be cited as sources of pain and or evidence of possible infection. Treatment of the underlying cause can restore normative function. Please see the section on Painful Ejaculation later in this chapter for a more through explanation of diagnosis and treatment of this condition.

Endocrine

The hormonal milieu is important for normal ejaculation. Hypogonadism was comorbid with DE at a rate of 26 % in a group of over 2400 men with sexual dysfunction [70]. Androgen receptors are present throughout the whole body including the areas of the brain associated with orgasm and arousal. Pelvic musculature may be dependent on testosterone mediated pathways [50]. Testosterone levels are related to ejaculatory disturbances where higher levels can be found in those with premature ejaculation and lower levels in delayed ejaculation [71]. Several studies have examined the role of testosterone levels in various ejaculatory disorders and have found that levels vary widely. This hormonal mismatch can be associated with DE resulting in decreased quality of life [72, 73]. However, a recent multicenter, randomized, double blind, placebo control trial revealed T normalization in hypogonadal men showed no significant improvement in ejaculation dysfunction including anejaculation, delayed ejaculation, reduced ejaculate volume, or ejaculation satisfaction [74]. The authors state that androgen deficiency is not the sole contributor to ejaculatory dysfunction. They also speculate that perhaps testosterone levels were not titrated high enough to see an overall benefit in the trial.

DE might also be associated with thyroid hormone levels. Thyroid hormones are believed to have a possible role in controlling contractions of the seminal vesicles and ejaculatory musculature. Hyperthyroidism is associated with premature ejaculation and hypothyroidism is associated with DE [75].

Prolactin may be a surrogate marker of serotonergic activity, hence elevated prolactin levels limit not only be linked to low testosterone levels, but also to ejaculatory dysfunction [50, 76]. Prolactin and dopamine are inversely related. As dopamine rises (as what happens with climax and orgasm) prolactin is suppressed. After orgasm, prolactin spikes while dopamine is suppressed. Prolactin is thought to be partly responsible for the refractory period in men after orgasm [77, 78]. Routine hormonal testing investigating perturbations of testosterone, prolactin and thyroid levels should be considered in patients with ejaculatory dysfunction and corresponding disease symptomatology (See Appendices 25.1 and 25.2 for suggested treatment algorithms.).

Pharmacology

DE can occur as a side effect of pharmacological therapy, thus it is imperative to routinely investigate patient medications as a part of the workup for DE. A well known and common side effect of the selective serotonin receptor inhibitors (SSRIs) is a sevenfold increased risk of DE. Hence, SSRIs are commonly used in an off-label fashion for the treatment for premature ejaculation as described earlier in the chapter [79, 80]. IELT is delayed with these drugs due to the serotonergic tone and receptor activation on the central nervous system [50]. There are also many other medications that can result in DE (Table 25.2).

Anti-psychotic medications such as risperidone, olanzapine, clozapine, and quetiapine can all cause sexual dysfunction in the form of decreased libido, arousal, and anorgasmia. These medications can result in decreased dopaminergic tone in the hypothalamus and hyperprolactinemia from excess prolactin secretion [81]. Quetiapine is thought to have less prolactin stimulating effect. Amantadine, bromocriptine, and cabergoline are medications that help control for hyperprolactin states. Regulation of prolactin may help correct testosterone levels which may help restore normal sexual function and ejaculation.

Psychological

Dissatisfaction, performance anxiety, and relationship distress can be both causes and effects of DE [54, 56, 82]. Although some may enjoy longer coital practices, delay in ejaculation may not

Table 25.2 Medications known to affect male ejaculation

Alcohol	Clomipramine	Lorazepam	Phentolamine
Alprazolam	Desmethylimipramine	Mirtazapine	Phenelzine sulfate
Aminocaproic acid	Fluoxetine[a]	Mesoridazine	Prazosin
Amitriptyline	Fluvoxamine	Methadone	Protriptyline
Amoxapine	Guanadrel	Methyldopa	Reserpine
Baclofen	Guanethidine	Naproxen	Sertraline[a]
Bethanidine	Haloperidol	Nortriptyline	Thiazide diuretics
Butaperazine	Hexamethonium	Pargyline	Thioridazine
Chlordiazepoxide	Imipramine	Paroxetine[a]	Trazodone
Chlorimipramine	Iproniazid	Perphenazine	Trifluoperazine
Chlorpromazine	Isocarboxazid	Phenothiazine	
Chlorprothixene	Labetalol	Phenoxybenzamine	

[a]All selective serotonin reuptake inhibitors (SSRIs)
Data from refs. [40, 46, 50, 52, 123]

only cause potential discomfort for the patient in terms of penile pain and abrasions; but also for the partner who may feel that the patient does not love them or find them attractive. It is not uncommon for men to "fake" orgasm to help their partner feel accepted and secure when in fact, the male is actually experiencing DE. Distress increases when infertility results from lack of ejaculation within a relationship [56].

Multiple proposed psychological underpinnings of DE include fear of pregnancy, fear of "defiling" a partner through ejaculation, suppressed anger, and unwillingness to accept pleasure [55, 56]. Four diverse psychological theories based on empirical support explaining DE involve: (1) insufficient stimulation (mental and physical), (2) masturbation (too frequent, idiosyncratic style, and incongruence between fantasy and reality), (3) psychic conflict (fear, anxiety, guilt from religious upbringing, loss of self with ejaculation, etc.) and (4) subtle desire disorder concealed as ejaculatory dysfunction (autosexual orientation, partner's touch is inhibiting, compulsion to satisfy partner, etc.) [83] (See Appendix 25.2 for sexual therapies.).

Physical and mental/emotional stimulation are important components of the normal male sexual cycle. DE can result if sufficient stimulation is not achieved in both of these areas. In one study of males with a malleable penile prosthesis there was a 10 % prevalence of DE [84]. This study demonstrates that although penile erections could be simulated, orgasm and ejaculation were still impaired. Despite the overly simplistic misconception that male sexual arousal is defined solely by erectile quality, a pathologic "disconnect" between the quality of mechanically induced erections (from VED, penile implants, etc.) and cognitive arousal often exists.

In a recent United States epidemiological study by the Global Online Sexuality Survey, it was found that 76.1 % of the 1133 English speaking men with mean age of 52 years with Facebook accounts admitted to masturbation [85]. Other studies indicate that 92 % of all men masturbate [43, 86]. Although masturbation has not been linked to any significant problems for the general population, the frequency, intensity, style, and fantasy associated with the practice has been attributed to ejaculatory problems. Idiosyncratic masturbation style refers to an individual's technique that involves the combination of pressure, speed, duration, and intensity needed to achieve an ejaculation and orgasm which is not reproducible with a partner using hands, mouth, and/or vagina [83, 87]. Men who practice this type of masturbation have a higher rate of sexual dysfunction [86, 88]. Some in the popular media has proposed that masturbation with pornography use and addiction can subsequently lead to sexual dissatisfaction and delayed ejaculation [89]. Recent studies have demonstrated that

pornography-related masturbation in coupled men is associated with decreased sexual desire [90]. This could potentially lead to DE based on lack of mental/emotional stimulation.

Psychic conflict is a cluster of issues that causes psychological opposition to ejaculation, mostly from fear. Fear of becoming a father, fear that the female genitals may harm them, shame from religious beliefs, fear of hurting, or anger towards their partner can all manifest in DE and sexual dysfunction [83]. Anxiety disorders and loss of sexual confidence can also occur in these individuals.

Subtle desire disorder is a group of disorders that mimic other diagnoses, making the treatment more difficult. An example of this condition would be a man with DE who enjoys self-sex more than partnered sex (autosexual orientation). Affected individuals are commonly inhibited by partners' touch and/or may feel the need to please their partners due to the diminutive effect of partnered sex compared to autoarousal and ejaculation. In the absence of mental/emotional arousal, these men may experience natural erections that have decreased penile sensation leading to DE [83].

Assessment

When evaluating for DE, patients should all have full medical and sexual histories performed along with detailed physical exams. Urologists may feel uncomfortable with the level of sexual detail that is warranted in obtaining a full sexual history. Understanding the cultural context and history of the disorder; the quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; the partners' assessment of the disorder and if the partner suffers from any sexual dysfunction her/himself; and the overall satisfaction of the sexual relationship are all important to garner during history taking [91]. Investigation by a sexual therapist is often required to help get a complete psychological evaluation. It is incumbent for the urologist to diagnosis medical pathologies that cause or contribute to DE such as assessing the hormonal milieu, anatomy, and overall medical conditions. Good communication between sexual therapist and medical practitioner is paramount to successful diagnosis and treatment of DE.

Appendix 25.1 provides an algorithm which helps to differentiate between retrograde ejaculation, delayed ejaculation, and ejaculatory duct obstruction, with subsequent treatment recommendations in Appendix 25.2.

Treatment

The workup and treatments for DE vary based on its definition and etiology. Knowing that a patient has secondary DE would trigger an investigation into his medications, quality of his sexual relationship and partners' health. Partner's health is an important factor as DE may be caused by fear of hurting her or decrease in sexual attractiveness if she had a mastectomy, hysterectomy or other types of disfigurements. Patients with anatomical abnormalities (unilateral or bilateral absences of vas for example) may need additional imaging looking for corresponding renal abnormalities or transrectal ultrasound to evaluate for ejaculatory structure defects. Signs of infection (prostatitis, hematospermia, lower urinary tract symptoms) should be evaluated with treatment of underlying medical conditions. Similarly, neurologic conditions such as spinal cord injury or multiple sclerosis should be addressed [42]. If a man is able to ejaculate with masturbation only it would be important to assess for an idiosyncratic masturbatory style [56].

A recent study by Mulhall et al. shows the importance and relative success with goal directed medical therapy targeted towards etiologies of DE. These authors found that 34 % of men had DE pathology due to SSRI therapy, among which 82 % of those who had SSRI cessation improved and 34 % of those who had medication adjustment improved. These authors also found that 35 % of men with DE had abnormal penile sensation, of which 60 % got better with penile vibratory stimulation (Please see Penile Vibratory Stimulation later in this chapter for details.).

Fifteen percent of men with DE were hypogonadal, and 24 % of them improved with hormonal treatment. Psychogenic issues were the root cause in 16 % of men with DE [92]. Of note, when a psychogenic cause is found, sexual therapy traditionally has had a much higher success rate than treatment of non-psychogenic causes [55, 56].

Treatments for DE can be broken down into medications, penile vibratory stimulation, psychological (sexual therapy, masturbation retraining, etc.), and the "sexual tipping point" model that incorporates the balancing of the biologic, psychological, social, and behavioral aspects that contribute to the disorder.

Pharmocology

Pharmacologic agents have been used to treat DE with varied success. Unfortunately, there is no FDA approved medication to treat DE as the majority of cited research is based on case and cohort studies that have been non-randomized, non-blinded, and non-placebo controlled. Many drugs have been used as both treatment and/or antidotes to other medications causing DE. The majority of the drugs that are used for DE are classified as anti-serotonergic, alpha-2 adrenergic antagonist or central dopaminergic medications. A recent survey of sexual health providers demonstrated an overall treatment success of 40 % with most providers commonly using cabergoline, bupropion, and oxytocin for treatments [93]. However, this survey measured anecdotal results of practitioners and there was no proven efficacy or superiority of any drug due to a lack of placebo controlled, randomized, blinded, comparative trials. All medications that have been suggested for therapeutic intervention can be found in Table 25.3 along with suggested DE dosing, the overall indication of the agent and the side effects of these medications (black box warning, serious side effects, and most common side effects) [40, 42, 46, 50, 52, 91, 94–96].

Cyproheptadine

This is a serotonin (5-HT) antagonist and antihistamine used to treat allergic rhinitis and anorexia nervosa. It has demonstrated shorter refractory periods and increased sexual activity in male rats [97]. Cyproheptadine was successfully used as an antidote at doses of 2–16 mg as needed or chronically to help counter the effects of SSRIs in humans [98]. In non-controlled case studies, cyproheptadine may reverse the sexual side effects of DE or anorgasmia of citalopram, nortriptyline, fluoxetine, fluvoxamine, imipramine, and clomipramine [99–102]. This drug's most frequent side effects include somnolence and poor tolerability. In addition, it may reverse the effects of the antidepressant or anti-obsessive properties of SSRIs [103].

Alpha-1-Adrenergic Agonists

Medications that act as agonists to the alpha-1-adrenergic receptors have typically been used for nasal congestion, hypotension, and acute bronchospasm. Pseudoephedrine, ephedrine, and midodrine have been shown to aid in the emission process and result in antegrade ejaculation [96]. Their mechanism is thought to be from stimulation of the sympathetic tone and closure of the bladder neck. Midodrine was shown to have nearly 60 % efficacy in treating and/or reversing anejaculation [104]. Patients with multiple sclerosis had the greatest response; those with bilateral sympathectomies had the least response.

Amantadine

This central dopaminergic agonist is used to treat the flu, Parkinsonism, and extra pyramidal symptoms. In rats, chronic amantadine administration induced shorter refractory periods and increased sexual frequency with no change in arousal [105]. Taking this drug 5–6 h before sex in humans has been suggested to help treat DE caused by SSRIs at a dose of 100 mg [42, 106].

Cabergoline

Cabergoline is a dopamine 2 agonist that inhibits prolactin secretion and is used for the purpose of treating hyperprolactinemia. In Parkinson's disease it was shown to enhance erections and orgasms with a decrease in refractory period [107]. In a single-blinded, placebo-controlled, crossover study between protirelin (prolactin stimulant) and cabergoline, cabergoline decreased the refractory period and lowered prolactin levels [108].

Table 25.3 Drug therapy for delayed/inhibited ejaculation[a]

Drug generic/(trade)	Delayed ejaculation dosage (not FDA approved indication)		Indication (FDA approved)	Side effects (at therapeutic FDA indication dose)
	As needed	Daily		
Cyproheptadine[b] (Periactin)	4–12 mg (3–4 h prior to sex)	–	• Allergic rhinitis • Urticarial • Anorexia nervosa	**Nausea**, **dizziness, urinary retention, photosensitivity, rash, abdominal pain, fatigue**, agranulocytosis, thrombocytopenia, heat stroke
Oxytocin[c] (Pitocin)	24 IU intranasal during sex or SL prior to sex	–	• Labor induction • Abortion adjunct • Postpartum hemorrhage	**Nausea, vomiting**, hypertension, afibrinogenemia, SAIDH Not for elective labor induction[d]
Pseudoephedrine[e] (Sudafed)	60–120 mg (120–150 min prior to sex)	–	• Nasal congestion	**Insomnia, anxiety, nausea, insomnia, tremor, urinary retention, headache, palpitations,** arrhythmias, hypertension
Ephedrine[e]	15–60 mg (1 h prior to sex)	–	• Acute bronchospasm • Hypotension	**Nausea, headache, dizziness, insomnia, hypertension, tremor, urinary retention, anxiety, palpitations,** arrhythmias, stroke, seizures, MI, nephrotoxicity, hepatotoxicity
Midodrine[e] (Orvaten, ProAmatine)	5–40 mg daily (30–120 min. prior to sex)	–	• Orthostatic hypotension	**Dysuria, paresthesia, rigors, pruritis, piloerection, rash,** bradycardia, erythema multiforme, visual field defect Supine elevated blood pressure[d]
Apomorphine (Apokyn)	0.5–1.5 mg intranasal (20 min before sex)	–	• Parkinson Ds	**Yawning, dyskinesia, rhinorrhea, hallucinations, anxiety, UTI, chest pain, diaphoresis,** hypotension, syncope, MI, priapism, abuse potential, hallucinations
Bethanechol[b] (Urecholine)	20 mg po (1–2 h prior to sex)	–	• Urinary retention • Neurogenic bladder • GERD • TCA adjunct treatment • Phenothiazine adjunct Tx	**Abdominal pain, nausea, diarrhea, headache, urinary urgency, malaise, flushing, miosis,** bronchospasm, hypotension, tachycardia, seizures
Amantadine[b] (Symmetrel)	100–400 mg (for 2 days prior to sex)	75–100 mg BID or TID	• Influenza A Tx and prophylaxis • Extrapyramidal sx • Parkinsonism	**Nausea, dizziness, depression, anorexia, hallucinations, compulsivity, hypotension, abnormal dreams, headache, constipation/diarrhea,** arrhythmias, psychosis, coma, impaired vision, pulmonary edema, neutropenia, seizure, heat stroke
Bupropion[b] (Wellbutrin, Zyban, Budeprion, Forfivo)	–	75 mg BID or TID	• Major depressive disorder • Seasonal affective disorder • Smoking cessation • Attention deficit-hyperactivity disorder (ADHD)	**Palpitations, urinary frequency, blurred vision, chest pain**, agitation, psychosis, hallucinations, seizures, hepatotoxicity, HTN, arrhythmias Suicidality, neuropsychiatric symptoms[d]

(continued)

Table 25.3 (continued)

Drug generic/(trade)	Delayed ejaculation dosage (not FDA approved indication)		Indication (FDA approved)	Side effects (at therapeutic FDA indication dose)
	As needed	Daily		
Buspirone[b] (BuSpar)	–	5–15 mg BID	• Anxiety	**Dizziness, nausea, headache, fatigue, blurred vision, numbness, weakness, abdominal pain, insomnia,** serotonin syndrome, tardive dyskinesia, sytonia, hostility, depression
Yohimbine (Yocon)	–	5.4 mg TID	• Impotence	**Urinary retention, hyperglycemia, tachycardia, irritability, tremor, nausea, dizziness, headache, flushing, diaphoresis, hypertension,** respiratory depression
Cabergoline[c] (Dostinex)	–	0.25–2 mg twice a week	• Hyperprolactinemia	**Nausea, dizziness, fatigue, abdominal pain, somnolence, anxiety, vertigo hot flashes, flatulence, breast pain, compulsivity,** orthostatic hypotension, pleural effusion, retroperitoneal fibrosis, depression, psychosis, pulmonary and pericardial fibrosis
Loratadine[b] (Claritin, Alavert)	–	10 mg daily	• Allergic rhinitis • Chronic idiopathic urticaria	**Drowsiness, fatigue, headache, dry mucous membranes, pharyngitis,** bronchospasm, hepatotoxicity, syncope, seizures, thrombocytopenia
Roboxetine (not available in USA)	–	4–8 mg	• Major depressive disorder • Panic disorder • Attention deficit-hyperactivity disorder (ADHD)	**Insomnia, nausea, excessive sweating, constipation, urinary tract infection, dysuria, urinary retention, ejaculatory pain,** tachycardia, blood pressure changes
Imipramine[e] (Tofranil)	–	25–75 mg daily	• Depression • Chronic pain	**Drowsiness, dizziness, blurred vision, palpitations, increase appetite, weakness, confusion, anxiety, impotence, galactorrhea, gynecomastia, photosensitivity, change in libido**, hypotension, syncope, QT prolongation, AV block, MI, stroke, seizures, ataxia, leukopenia, hallucinations, depression, hepatitis, angioedema, heat stroke, psychosis, withdrawal symptoms Suicidality[d]

Bold terms represent more common reactions and unbolded terms represent serious reactions
Data from refs. [42, 95, 96, 121, 123]
[a]None of these drugs are FDA approved for delayed ejaculation
[b]Works in part as a possible antidote for SSRI and SSNRI for sexual side effect of DE
[c]May help when abnormalities of Prolactin or other hormonal issues considered
[d]Black box warning
[e]Known to help with retrograde ejaculation

This study also showed evidence of improvement in both ejaculation and libido. Other authors have found similar outcomes with anorgasmic men [96]. Some providers have described anecdotal success with cabergoline [93]. It is hypothesized that when prolactin levels are elevated or high normal at baseline, cabergoline can be a good first choice. Low or normal prolactin levels prompt some providers to then use oxytocin as their first line agent.

Oxytocin

Oxytocin is a non-peptide hormone that has been shown to have effect in many areas in men. In women it has been used to induce uterine contraction and lactation during nursing. In men it has been shown to increase ejaculation, paternal nurturing, long-term romantic bonds and attachments, stimulation of sexual desire and conditioning of the sexual experience in preparation of ejaculation and orgasm [109]. Oxytocin surges during male ejaculation, orgasm, and detumescence, returning to baseline by 10 min after surge [71].

Bupropion

This is a dopamine and norepinephrine reuptake inhibitor that is used to treat depression, smoking addiction, and attention-deficient-hyperactivity disorder. It can be used as an antidote to the side effects of sexual dysfunction and DE associated with SSRIs and has been shown effective in humans [103, 110]. Daily or as needed bupropion resulted in a complete reversal or improvement of negative sexual side effects in 66–69 % of patients on SSRIs [111].

Buspirone

The anxiolytic buspirone binds to serotonin and dopamine 2 receptors. It has been used to treat the side effects of sexual dysfunction associated with SSRIs [112]. Buspirone was shown to be effective in patients with generalized anxiety and sexual dysfunction in ranges of 16–60 mg daily [94].

Yohimbine and Herbal Supplements

Yohimbine is a plant derivative herbal supplement used for decreased libido and ejaculatory dysfunction. Rat models of ejaculatory exhaustion demonstrated nullification of refractory periods and reinitiation of the ejaculation motor reflex after intravenous yohimbine administration [113]. In another study, men treated with Fluoxetine for 2 years were given yohimbine. This countered the effect of the SSRI on orgasm and ejaculation [114]. Multiple studies in humans have found yohimbine to help treat ejaculatory and orgasmic dysfunction along with other sexual dysfunction; however, these studies have not been performed in large blinded, randomized, or placebo-controlled fashion [42, 50, 96, 98, 115].

Yohimbine, horny goat weed, MACA root, tribulus terrestris, and saffron are all ancient herbal medicines that have been used for thousands of years in Chinese, Indian, ancient Egyptian, Roman, and Greek cultures to help treat all forms of ejaculatory dysfunction. The use of these particular medications has been tested in animal models and in human research, and these studies have shown some evidence towards decreased ejaculatory latency periods [116].

Bethanechol

Bethanechol is an FDA approved drug used for urinary retention, gastroesophageal reflux disease, and as an adjuvant for tricyclic antidepressants and phenothiazines. Bethanachol is a cholinergic agonist that increases detrusor and gastrointestinal motility and has been shown to help reverse the DE effects of protriptyline, amoxapine, and imipramine [46, 117, 118].

Apomorphine

Apomorphine is a central and a peripheral stimulator of postsynaptic dopamine 2 receptors used for hypomobility in Parkinson disease. Rat studies showed increased activity of the sympathetic branches of the hypogastric nerve innervating the vas deferens resulting in neuronal activity that occurs during sexual climax [119]. This has been shown to excite the nerve patterns in the lumbosacral plexus associated with ejaculation. Although the drug is commonly administered subcutaneously, it seems to have equal efficacy on sexual function intranasally in experiments [120]. Episodic doses in humans have been successful in patients who were using it for sexual dysfunction including erectile dysfunction [121].

Others

The intermittent use of other drugs has shown to help reverse the DE effect of SSRIs, which include amphetamines [122] and loratadine (10 mg daily) [95]. In addition, alpha-1 adrenergic receptor agonists like imipramine and pseudoephedrine may be of limited utility for retrograde ejaculation [123]. Reboxetine is a selective noradrenaline reuptake inhibitor that can be used as an alternative to SSRI for depression and is thought to have less sexual side effects. However, there are reports of spontaneous ejaculation with the use of this drug [124–126]. Alterations of SSRI regimens in addition to antidotes can be effective in treatment of DE [127, 128]. Additional drugs that may help DE are ropinirole, pramipexole, and flibanserin [50].

Penile Vibratory Stimulation (PVS)

Electro-ejaculation techniques have been used for many years to treat ejaculatory problems in neurogenic patients who present for infertility. Ejaculation can be obtained via stimulation to the pudendal nerves which helps to initiate the ejaculatory reflex [129]. In DE patients, PVS has been used on the frenulum for certain time periods to help increase the sensation to the penis allowing for the ejaculatory reflex to be triggered. It has been shown to work with secondary DE at a rate of 62 % [130]. For men with multiple sclerosis, PVS has also been shown to be helpful [131]. Combining PVS with medical therapy increases the efficacy of DE treatment. However, to date there have been no studies that are either placebo-controlled or randomized [50].

Psychological

Psychological treatments include but are not limited to: sexual education; retraining masturbatory practices; increased genital specific stimulation; role-playing on his own and in front of his partner; anxiety reduction on ejaculation and performance; and recalibrating the mismatch of sexual fantasies with arousal (such as with pornography use and fantasy stimulation compared to reality) [91]. Men and women can realistically evaluate their sexual practice and manage expectations by having a basic understanding of the sexual cycle for their respective partners. Masturbation can be considered practice for the real performance for greater psychosexual arousal to orgasm for both parties [55]. Although fantasy can be harmful when not associated with appropriate sexual arousal, fantasy can be quite helpful if it allows blockage of critical thoughts that may be preventing orgasm and ejaculation. The reduction of anxiety as a component of DE is very important as performance anxiety often interrupts the natural ejaculatory and orgasmic progression [132]. A well-trained sexual therapist can be invaluable for these treatments to work. Other addressable psychopathologies that may be masquerading or comorbid with DE can be uncovered via sex therapy. Female sexual dysfunction can contribute to DE in men so evaluation of this is a critical part of treatment. Referral to a properly qualified therapist, psychiatrist or psychologist is appropriate and often times warranted (See Appendices 25.1 and 25.2).

Sexual Tipping Point Model

Dr. Michael A. Perelman has written extensively on the multifactorial etiology of DE and "The Ejaculatory Tipping Point" which is a dynamic process. Dr. Perelman theorizes that every man has a multidimensional predetermined ejaculatory threshold that will result in tipping the "scale" of balancing factors towards ejaculation and orgasm. In his model he has a scale balancing the excitatory and inhibitory factors between the physiologic and organic issues and the psychosocial and behavior issues. Deciphering between the biogenic and psychosocial factors is the goal of both the patient and the clinician in helping achieve the desired outcome whether they suffer from premature ejaculation, delayed ejaculation, or anorgasmia [55, 133]. The sexual tipping point has been embraced as a holistic approach to ejaculatory dysfunction as it incorporates all aspects of the disorder to help find solutions [50].

Painful Ejaculation

Etiology

Painful ejaculation is perhaps the least well-studied and characterized of the ejaculatory disorders discussed in this chapter. This condition can have a dramatically negative impact on relationships, leading to the avoidance of sexual intimacy with one's partner, sexual distress, sexual dissatisfaction, and ultimately, marital problems [134, 135]. A variety of causes have been cited, but the underlying etiology is not well understood. Some authors suggest spasm of the bladder neck or dystonia of the pelvic floor musculature during orgasm [136], and others note that ejaculatory duct obstruction may be the underlying cause [26, 137]. This obstruction could arise from ejaculatory duct calculi, intrinsic stenosis, or external compression by a prostatic cyst leading to ejaculatory duct compression and blockage. Antolak et al. have suggested that pudendal nerve compression and neuropathy may be the cause of ejaculatory pain in some men [138]. Finally, some authors have suggested that antidepressant medications may induce painful ejaculation as a side effect [139–143].

The true incidence of painful ejaculation is unclear. Most studies assessing this condition employ retrospective questionnaires, and are thus subject to some form of bias. In 2003, Rosen et al. reported that 6.7 % of men participating in a large multinational survey of aging males noted pain or discomfort on ejaculation [2]. Roberts et al. found that 1.5 % of the 2115 respondents from Olmsted County, Minnesota experienced ejaculatory pain [144]. Another US study reported that 9.7 % of respondents (age 20- to 74-years-old) noted perineal pain or discomfort with ejaculation [67, 145]. Finally, the authors who developed the National Institutes of Health Chronic Prostatitis Symptom Index found that ejaculatory pain was present in 58 % of men with prostatitis, 17 % of men with BPH, and 4 % of controls [146].

Diagnosis

The diagnosis of ejaculatory pain is largely based on subjective complaints; objective diagnostic information can be gathered in some instances. For example, in men with ejaculatory duct obstruction, transrectal ultrasound imaging can be utilized to visualize ejaculatory duct anatomical abnormalities (such as calculi or a compressing cyst) and/or seminal vesicle dilation (a possible sign of distal ejaculatory duct obstruction). Antidepressant medication-related symptoms may be clarified by converting to another medication or ceasing this therapy (in conjunction with the prescribing physician). In patients with suspected pudendal neuropathy, neurophysiological tests may help delineate pudendal neuropathy associated with perineal pressure [147]. Most of the purported causes of ejaculatory pain, however, are more challenging to diagnose and not associated with clear physical findings or alterations in laboratory values. This fact can make pursuit of a clear therapeutic plan challenging for both the patient and the treating physician.

Treatment

The treatment of painful ejaculation should be based on objective findings from the examination and laboratory workup. Prostatitis and urinary tract infections should be treated. Patients with ejaculatory duct obstruction should be considered for transurethral resection of the ejaculatory duct. Patients with seminal vesicle anomalies (i.e., seminal vesicle stone) suspected of being the root cause of the pain should be informed of the option of laparoscopic seminal vesicle excision, as this has been reported as providing durable relief in the setting of ejaculatory pain [148]. Finally, consideration should be given for enlisting the assistance of physical therapists specializing in pelvic floor physical therapy. Anderson et al. reported encouraging results with trigger

point release and paradoxical relaxation training in 133 men with refractory chronic pelvic pain syndrome and sexual dysfunction (ejaculatory pain [56 %], decreased libido [66 %], erectile and ejaculatory dysfunction [31 %]) [149]. The authors noted significant improvement in the above categories of sexual dysfunction, with 70 % of patients reporting markedly or moderately improved symptoms after trigger point release/paradoxical relaxation training. Thus, physical therapists can help elicit and treat underlying musculoskeletal anomalies, which may be the root cause of many patients' complaints of ejaculatory pain.

Conclusions

The physiology of ejaculation is highly integrated and relies on both the sympathetic and parasympathetic neural pathways. Ejaculatory dysfunction is fairly common and is a source of significant bother for many of those affected. Ejaculatory dysfunction can entail a wide array of anomalies, including premature ejaculation, inhibited ejaculation (consisting of delayed ejaculation and absent ejaculation), and painful ejaculation. Patients should be evaluated through a thorough medical history, physical examination, and laboratory testing to help ensure proper diagnosis. Finally, with directed therapy, many disorders of ejaculation can be successfully treated.

Appendices

Appendix 25.1

Algorithm of Disordered Ejaculation in Men. $^{\Psi}$=See Collaboration of Clinician and Sexual Therapist (Appendix 25.2). *=Medications in Table 25.3 can be tried in treatment of Retrograde Ejaculation (see Table 25.3). ^ = If patient on SSRI consider use of SSRI Antidote types of medications (see Table 25.3). †=Medications in Table 3 can be used for Prolactin abnormalities (see Table 25.3).

(Used with permission from Sadowski DJ, Butcher MJ, Kohler TS. Delayed Ejaculation: Medical and Psychological treatments and Algorithms. Current Sexual Health Reports. September 2015; 7(3): 170–179. Created using data in Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. The journal of sexual medicine. 2010;7(4 Pt 2):1668–86.)

Appendix 25.2

Collaboration of Clinician and Sexual Therapist (Used with permission from Sadowski DJ, Butcher MJ, Kohler TS. Delayed Ejaculation: Medical and Psychological treatments and Algorithms. Current Sexual Health Reports. September 2015; 7(3): 170–179. Created using data from Perelman, MA. Delayed ejaculation in: Principles and practice of sex therapy. Fifth edition. Binik YM, Hall KSK. (eds). New York, NY: The Guilford Press; 2014. 138–55.)

References

1. Masters WH, Johnson VE. Human sexual response. Little, Brown and Company: Boston, MA; 1966.
2. Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). Eur Urol. 2003; 44(6):637–49.
3. Giuliano F, Clement P. Physiology of ejaculation: emphasis on serotonergic control. Eur Urol. 2005;48(3):408–17.
4. Newman HF, Reiss H, Northup JD. Physical basis of emission, ejaculation, and orgasm in the male. Urology. 1982;19(4):341–50.
5. Barnas JL, Pierpaoli S, Ladd P, Valenzuela R, Aviv N, Parker M, et al. The prevalence and nature of orgasmic dysfunction after radical prostatectomy. BJU Int. 2004;94(4):603–5.
6. Schlegel PN, Walsh PC. Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. J Urol. 1987;138(6):1402–6.
7. Keast J. Autonomic Ganglia. In: McLachlan E, editor. Pelvic ganglia. Luxemburg: Harwood Academin; 1995. p. 445–79.
8. Ver Voort SM. Ejaculatory stimulation in spinal-cord injured men. Urology. 1987;29(3):282–9.

9. Amelar RD, Hotchkiss RS. The split ejaculate: its use in the management of male infertility. Fertil Steril. 1965;16:46–60.
10. McKenna KE, Chung SK, McVary KT. A model for the study of sexual function in anesthetized male and female rats. Am J Physiol. 1991;261(5 Pt 2): R1276–85.
11. Truitt WA, Coolen LM. Identification of a potential ejaculation generator in the spinal cord. Science. 2002;297(5586):1566–9.
12. Allard J, Truitt WA, McKenna KE, Coolen LM. Spinal cord control of ejaculation. World J Urol. 2005;23(2):119–26.
13. Coolen LM, Allard J, Truitt WA, McKenna KE. Central regulation of ejaculation. Physiol Behav. 2004;83(2):203–15.
14. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537–44.
15. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. J Epidemiol Community Health. 1999;53(3):144–8.
16. Masters WH, Johnson VE. Human sexual inadequacy. London: Churchill; 1970. p. xi–467.
17. Waldinger MD, Schweitzer DH. Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part I – validity of DSM-IV-TR. J Sex Med. 2006;3(4):682–92.
18. Symonds T, Perelman M, Althof S, Giuliano F, Martin M, Abraham L, et al. Further evidence of the reliability and validity of the premature ejaculation diagnostic tool. Int J Impot Res. 2007;19(5):521–5.
19. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. Am J Psychiatry. 1994;151(9):1377–9.
20. Patrick DL, Althof SE, Pryor JL, Rosen R, Rowland DL, Ho KF, et al. Premature ejaculation: an observational study of men and their partners. J Sex Med. 2005;2(3):358–67.
21. Rowland DL, Cooper SE, Schneider M. Defining premature ejaculation for experimental and clinical investigations. Arch Sex Behav. 2001;30(3):235–53.
22. Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Proposal for a definition of lifelong premature ejaculation based on epidemiological stopwatch data. J Sex Med. 2005;2(4):498–507.
23. Dinsmore WW, Ralph DJ, Kell P, Wylie KR, Dean JP, Novak C, et al. Evaluation of the sexual assessment monitor, a diagnostic device used to electronically quantify ejaculatory latency time: findings from three studies. BJU Int. 2006;98(3):613–8.
24. Lue TF, Giuliano F, Montorsi F, Rosen RC, Andersson KE, Althof S, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2004;1(1):6–23.
25. Sharlip ID. Guidelines for the diagnosis and management of premature ejaculation. J Sex Med. 2006;3 Suppl 4:309–17.
26. Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, et al. AUA guideline on the pharmacologic management of premature ejaculation. J Urol. 2004;172(1):290–4.
27. Colpi GM, Fanciullacci F, Beretta G, Negri L, Zanollo A. Evoked sacral potentials in subjects with true premature ejaculation. Andrologia. 1986;18(6): 583–6.
28. Fanciullacci F, Colpi GM, Beretta G, Zanollo A. Cortical evoked potentials in subjects with true premature ejaculation. Andrologia. 1988;20(4): 326–30.
29. Shull GR, Sprenkle DH. Retarded ejaculation reconceptualization and implications for treatment. J Sex Marital Ther. 1980;6(4):234–46.
30. Semans JH. Premature ejaculation: a new approach. South Med J. 1956;49(4):353–8.
31. De Amicis LA, Goldberg DC, LoPiccolo J, Friedman J, Davies L. Clinical follow-up of couples treated for sexual dysfunction. Arch Sex Behav. 1985;14(6): 467–89.
32. Busato W, Galindo CC. Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. BJU Int. 2004;93(7):1018–21.
33. Henry R, Morales A. Topical lidocaine-prilocaine spray for the treatment of premature ejaculation: a proof of concept study. Int J Impot Res. 2003; 15(4):277–81.
34. Hull EM, Lumley LA, Matuszewich L, Dominguez J, Moses J, Lorrain DS. The roles of nitric oxide in sexual function of male rats. Neuropharmacology. 1994;33(11):1499–504.
35. McMahon CG, Stuckey BG, Andersen M, Purvis K, Koppiker N, Haughie S, et al. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. J Sex Med. 2005;2(3):368–75.
36. Pryor JL, Althof SE, Steidle C, Rosen RC, Hellstrom WJ, Shabsigh R, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. Lancet. 2006;368(9539):929–37.
37. Safarinejad MR. Safety and efficacy of dapoxetine in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. Neuropsychopharmacology. 2008;33(6): 1259–65.
38. Waldinger MD, Schweitzer DH. Premature ejaculation and pharmaceutical company-based medicine: the dapoxetine case. J Sex Med. 2008;5(4):966–97.
39. Kim JJ, Kwak TI, Jeon BG, Cheon J, Moon DG. Effects of glans penis augmentation using hyaluronic acid gel for premature ejaculation. Int J Impot Res. 2004;16(6):547–51.
40. Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F. Sexual medicine: sexual dysfunctions in

men and women. In: McMahon CG, Abdo C, Hull EM, Incrocci L, Levine L, Perelman MA, et al., editors. Plymouth, MA: Health Publications; 2004. p. 409–68.
41. American Psychiatric Association. Diagnostic criteria from DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000. p. 370, xii.
42. McMahon CG, Jannini E, Waldinger M, Rowland D. Standard operating procedures in the disorders of orgasm and ejaculation. J Sex Med. 2013;10(1): 204–29.
43. Kinsey AC, Pomeroy WB, Martin CE, New York Academy of Medicine. Sexual behavior in the human male. Philadelphia, PA: WB Saunders Co; 1948. p. 804, xv.
44. Rowland DL, Keeney C, Slob AK. Sexual response in men with inhibited or retarded ejaculation. Int J Impot Res. 2004;16(3):270–4.
45. Nathan SG. The epidemiology of the DSM-III psychosexual dysfunctions. J Sex Marital Ther. 1986;12(4):267–81.
46. Richardson D, Nalabanda A, Goldmeier D. Retarded ejaculation – a review. Int J STD AIDS. 2006;17(3): 143–50.
47. Spector IP, Carey MP. Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. Arch Sex Behav. 1990;19(4): 389–408.
48. Nazareth I, Boynton P, King M. Problems with sexual function in people attending London general practitioners: cross sectional study. BMJ. 2003; 327(7412):423.
49. McCabe MP, Connaughton C. Psychosocial factors associated with male sexual difficulties. J Sex Res. 2014;51(1):31–42.
50. Mulhall JP, Hsiao W. Men's sexual health and fertility: a clinician's guide. Nelson CJ, Brock D, Dean RC, editors. New York, NY: Springer; 2014.
51. Jannini EA, Simonelli C, Lenzi A. Sexological approach to ejaculatory dysfunction. Int J Androl. 2002;25(6):317–23.
52. Jannini EA, Simonelli C, Lenzi A. Disorders of ejaculation. J Endocrinol Invest. 2002;25(11):1006–19.
53. Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010;7(11):3572–88.
54. Abdel-Hamid IA, el Saleh S. Primary lifelong delayed ejaculation: characteristics and response to bupropion. J Sex Med. 2011;8(6):1772–9.
55. Perelman MA, Rowland DL. Retarded ejaculation. World J Urol. 2006;24(6):645–52.
56. Perelman MA. Delayed ejaculation. In: Binik YM, Hall KSK, editors. Principles and practice of sex therapy. 5th ed. New York, NY: The Guilford Press; 2014. p. 138–55.
57. Waldinger MD. Toward evidence-based genetic research on lifelong premature ejaculation: a critical evaluation of methodology. Korean J Urol. 2011;52(1):1–8.
58. Gregoire A. ABC of sexual health: assessing and managing male sexual problems. BMJ. 1999; 318(7179):315–7.
59. McMahon CG, Abdo C, Incrocci L, Perelman M, Rowland D, Waldinger M, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2004;1(1): 58–65.
60. Edwards AE, Husted JR. Penile sensitivity, age, and sexual behavior. J Clin Psychol. 1976;32(3): 697–700.
61. Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, Boolell M. A multinational population survey of intravaginal ejaculation latency time. J Sex Med. 2005;2(4):492–7.
62. Latini DM, Penson DF, Wallace KL, Lubeck DP, Lue TF. Clinical and psychosocial characteristics of men with erectile dysfunction: baseline data from ExCEED. J Sex Med. 2006;3(6):1059–67.
63. Gierveld Jde J, van Groenou MB, Hoogendoorn AW, Smit JH. Quality of marriages in later life and emotional and social loneliness. J Gerontol B Psychol Sci Soc Sci. 2009;64(4):497–506.
64. DasGupta R, Fowler CJ. Sexual and urological dysfunction in multiple sclerosis: better understanding and improved therapies. Curr Opin Neurol. 2002;15(3):271–8.
65. Enzlin P, Mathieu C, Van Den Bruel A, Vanderschueren D, Demyttenaere K. Prevalence and predictors of sexual dysfunction in patients with type 1 diabetes. Diabetes Care. 2003;26(2):409–14.
66. Minderhoud JM, Leemhuis JG, Kremer J, Laban E, Smits PM. Sexual disturbances arising from multiple sclerosis. Acta Neurol Scand. 1984;70(4):299–306.
67. Comarr AE. Sexual function among patients with spinal cord injury. Urol Int. 1970;25(2):134–68.
68. Xia JD, Han YF, Pan F, Zhou LH, Chen Y, Dai YT. Clinical characteristics and penile afferent neuronal function in patients with primary delayed ejaculation. Andrology. 2013;1(5):787–92.
69. Fletcher MS, Herzberg Z, Pryor JP. The aetiology and investigation of haemospermia. Br J Urol. 1981;53(6):669–71.
70. Corona G, Jannini EA, Mannucci E, Fisher AD, Lotti F, Petrone L, et al. Different testosterone levels are associated with ejaculatory dysfunction. J Sex Med. 2008;5(8):1991–8.
71. Corona G, Jannini EA, Vignozzi L, Rastrelli G, Maggi M. The hormonal control of ejaculation. Nat Rev Urol. 2012;9(9):508–19.
72. Paduch D, Polzer P, Ni X, Basaria S. Effects of testosterone solution 2 % for the treatment of ejauclatory dysfunction in androgen-deficient men. 20th Annual fall scientific meeting of SMSNA, 20–23 Nov 2014 Program Book. 2014(Abtract 003):53.
73. Paduch D, Polzer P, Morgentaler A, Althof SE, Ni X, Patel A, et al. Prevalence of ejaculatory dysfunction as a function of testosterone. 20th Annual fall scientific meeting of SMSNA, 20–23 Nov 2014 Program Book. 2014(Abstract 004):52.

74. Paduch D, Polzer P, Ni X, Basaria S. Testosterone replacement in androgen-deficient men with ejaculatory dysfunction: a randomized controlled trial. J Clin Endocrinol Metab. 2015;100(8):2956–62.
75. Carani C, Isidori AM, Granata A, Carosa E, Maggi M, Lenzi A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metab. 2005;90(12):6472–9.
76. Corona G, Petrone L, Paggi F, Lotti F, Boddi V, Fisher A, et al. Sexual dysfunction in subjects with Klinefelter's syndrome. Int J Androl. 2010;33(4):574–80.
77. Fitzgerald P, Dinan TG. Prolactin and dopamine: what is the connection? A review article. J Psychopharmacol. 2008;22(2 Suppl):12–9.
78. Kruger TH, Hartmann U, Schedlowski M. Prolactinergic and dopaminergic mechanisms underlying sexual arousal and orgasm in humans. World J Urol. 2005;23(2):130–8.
79. Corona G, Ricca V, Bandini E, Mannucci E, Lotti F, Boddi V, et al. Selective serotonin reuptake inhibitor-induced sexual dysfunction. J Sex Med. 2009;6(5):1259–69.
80. Kiev A, Feiger A. A double-blind comparison of fluvoxamine and paroxetine in the treatment of depressed outpatients. J Clin Psychiatry. 1997;58(4):146–52.
81. Keller R, Mongini F. Switch to quetiapine in antipsychotic agent-related hyperprolactinemia. Neurol Sci. 2002;23(5):233–5.
82. Rowland D, van Diest S, Incrocci L, Slob AK. Psychosexual factors that differentiate men with inhibited ejaculation from men with no dysfunction or another sexual dysfunction. J Sex Med. 2005;2(3):383–9.
83. Althof SE. Psychological interventions for delayed ejaculation/orgasm. Int J Impot Res. 2012;24(4):131–6.
84. Fathy A, Shamloul R, AbdelRahim A, Zeidan A, El-Dakhly R, Ghanem H. Experience with Tube (Promedon) malleable penile implant. Urol Int. 2007;79(3):244–7.
85. Shaeer O. The global online sexuality survey (GOSS): the United States of America in 2011 Chapter III – premature ejaculation among English-speaking male Internet users. J Sex Med. 2013;10(7):1882–8.
86. Bronner G, Ben-Zion IZ. Unusual masturbatory practice as an etiological factor in the diagnosis and treatment of sexual dysfunction in young men. J Sex Med. 2014;11(7):1798–806.
87. Perelman M. Idiosyncratic masturbation patterns: a key unexplored variable in the treatment of retarded ejaculation by the practicing urologist. J Urol. 2005;173:340. Abstract 1254.
88. Sank LI. Traumatic masturbatory syndrome. J Sex Marital Ther. 1998;24(1):37–42.
89. Rothbart D. He's just not that into anyone (cover story). New York, 2 Jul 2011, p. 83–8.
90. Carvalheira A, Traeen B, Stulhofer A. Masturbation and pornography use among coupled heterosexual men with decreased sexual desire: how many roles of masturbation? J Sex Marital Ther. 2014;1–10.
91. Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2010;7(4 Pt 2):1668–86.
92. Teloken P, Nelson C, Mullhall J. Outcomes with medical treatment of secondary delayed orgasm proposal of a clinical care pathway. J Urol. 2012;187(4 Suppl 1496):606.
93. Butcher M, Sadowski D, Botchway A, Welliver C, Kohler T. Delayed ejaculation remains a recalcitrant condition: results of a SMSNA survey. 20th Annual fall scientific meeting of SMSNA, 20–23 Nov 2014. Program Book. 2014(Abstract 041):70.
94. Porst H, Buvat J, Standards Committee of the International Society for Sexual Medicine. Standard practice in sexual medicine. McMahon CG, Waldinger M, Rowland D, Assalian P, Kim YC, Bechara A, et al., editors. Malden, Mass.; Oxford: Blackwell Pub. 2006. p. 188–209.
95. Aukst-Margetic B, Margetic B. An open-label series using loratadine for the treatment of sexual dysfunction associated with selective serotonin reuptake inhibitors. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(5):754–6.
96. Shin D, Spitz A. The evaluation and treatment of delayed ejaculation. Sex Med Rev. 2014;2(3-4):121–33.
97. Menendez Abraham E, Moran Viesca P, Velasco Plaza A, Marin B. Modifications of the sexual activity in male rats following administration of antiserotoninergic drugs. Behav Brain Res. 1988;30(3):251–8.
98. Ashton AK, Hamer R, Rosen RC. Serotonin reuptake inhibitor-induced sexual dysfunction and its treatment: a large-scale retrospective study of 596 psychiatric outpatients. J Sex Marital Ther. 1997;23(3):165–75.
99. Lauerma H. Successful treatment of citalopram-induced anorgasmia by cyproheptadine. Acta Psychiatr Scand. 1996;93(1):69–70.
100. Steele TE, Howell EF. Cyproheptadine for imipramine-induced anorgasmia. J Clin Psychopharmacol. 1986;6(5):326–7.
101. Sovner R. Treatment of tricyclic antidepressant-induced orgasmic inhibition with cyproheptadine. J Clin Psychopharmacol. 1984;4(3):169.
102. McCormick S, Olin J, Brotman AW. Reversal of fluoxetine-induced anorgasmia by cyproheptadine in two patients. J Clin Psychiatry. 1990;51(9):383–4.
103. DeBattista C, Solvason B, Poirier J, Kendrick E, Loraas E. A placebo-controlled, randomized, double-blind study of adjunctive bupropion sustained release in the treatment of SSRI-induced sexual dysfunction. J Clin Psychiatry. 2005;66(7):844–8.
104. Safarinejad MR. Midodrine for the treatment of organic anejaculation but not spinal cord injury: a prospective randomized placebo-controlled double-

blind clinical study. Int J Impot Res. 2009;21(4): 213–20.
105. Ferraz MM, Fontanella JC, Damasceno F, Silva de Almeida OM, Ferraz MR. Chronic amantadine treatment enhances the sexual behaviour of male rats. Pharmacol Biochem Behav. 2007;86(4):616–21.
106. Balon R. Intermittent amantadine for fluoxetine-induced anorgasmia. J Sex Marital Ther. 1996;22(4):290–2.
107. Wittstock M, Benecke R, Dressler D. Cabergoline can increase penile erections and libido. Neurology. 2002;58(5):831.
108. Kruger TH, Haake P, Haverkamp J, Kramer M, Exton MS, Saller B, et al. Effects of acute prolactin manipulation on sexual drive and function in males. J Endocrinol. 2003;179(3):357–65.
109. Veening JG, de Jong TR, Waldinger MD, Korte SM, Olivier B. The role of oxytocin in male and female reproductive behavior. Eur J Pharmacol. 2015;753: 209–28.
110. Labbate LA, Grimes JB, Hines A, Pollack MH. Bupropion treatment of serotonin reuptake antidepressant-associated sexual dysfunction. Ann Clin Psychiatry. 1997;9(4):241–5.
111. Ashton AK, Rosen RC. Bupropion as an antidote for serotonin reuptake inhibitor-induced sexual dysfunction. J Clin Psychiatry. 1998;59(3):112–5.
112. Landen M, Eriksson E, Agren H, Fahlen T. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. J Clin Psychopharmacol. 1999;19(3): 268–71.
113. Carro-Juareza M, Rodriguez-Manzo G. Yohimbine reverses the exhaustion of the coital reflex in spinal male rats. Behav Brain Res. 2003;141(1):43–50.
114. Jacobsen FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry. 1992;53(4):119–22.
115. Adeniyi AA, Brindley GS, Pryor JP, Ralph DJ. Yohimbine in the treatment of orgasmic dysfunction. Asian J Androl. 2007;9(3):403–7.
116. Melnyk J, Marcone M. Aphrodisiacs from plant and animal sources—a review of current scientific literature. Food Res Int. 2011;44:840–50.
117. Segraves RT. Reversal by bethanechol of imipramine-induced ejaculatory dysfunction. Am J Psychiatry. 1987;144(9):1243–4.
118. Yager J. Bethanechol chloride can reverse erectile and ejaculatory dysfunction induced by tricyclic antidepressants and mazindol: case report. J Clin Psychiatry. 1986;47(4):210–1.
119. Stafford SA, Coote JH. Activation of D2-like receptors induces sympathetic climactic-like responses in male and female anaesthetised rats. Br J Pharmacol. 2006;148(4):510–6.
120. Lu W, Jiang W, Chen J, Yin M, Wang Z, Jiang X. Modulation of brain delivery and copulation by intranasal apomorphine hydrochloride. Int J Pharm. 2008;349(1-2):196–205.
121. Kendirci M, Hellstrom WJ. Intranasal apomorphine. Nastech Pharmaceutical. Investig Drug J. 2004; 7(5):483–8.
122. Bartlik BD, Kaplan P, Kaplan HS. Psychostimulants apparently reverse sexual dysfunction secondary to selective serotonin re-uptake inhibitors. J Sex Marital Ther. 1995;21(4):264–71.
123. McMahon CG. Management of ejaculatory dysfunction. Intern Med J. 2014;44(2):124–31.
124. Haberfellner EM. Sexual dysfunction caused by reboxetine. Pharmacopsychiatry. 2002;35(2):77–8.
125. O'Flynn R, Michael A. Reboxetine-induced spontaneous ejaculation. Br J Psychiatry. 2000;177:567–8.
126. Sivrioglu EY, Topaloglu VC, Sarandol A, Akkaya C, Eker SS, Kirli S. Reboxetine induced erectile dysfunction and spontaneous ejaculation during defecation and micturition. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(2):548–50.
127. Taylor MJ. Strategies for managing antidepressant-induced sexual dysfunction: a review. Curr Psychiatry Rep. 2006;8(6):431–6.
128. Schweitzer I, Maguire K, Ng C. Sexual side-effects of contemporary antidepressants: review. Aust N Z J Psychiatry. 2009;43(9):795–808.
129. Sonksen J, Ohl DA, Wedemeyer G. Sphincteric events during penile vibratory ejaculation and electroejaculation in men with spinal cord injuries. J Urol. 2001;165(2):426–9.
130. Nelson CJ, Ahmed A, Valenzuela R, Parker M, Mulhall JP. Assessment of penile vibratory stimulation as a management strategy in men with secondary retarded orgasm. Urology. 2007;69(3):552–5. discussion 5–6.
131. Previnaire JG, Lecourt G, Soler JM, Denys P. Sexual disorders in men with multiple sclerosis: evaluation and management. Ann Phys Rehabil Med. 2014;57(5):329–36.
132. Lieblum S, Rosen R. Principles and practice of sex therapy. 2nd ed. New York, NY: Guilford Press; 2000.
133. Perelman MA. A new combination treatment for premature ejaculation: a sex therapist's perspective. J Sex Med. 2006;3(6):1004–12.
134. Rust J, Golombok S, Collier J. Marital problems and sexual dysfunction: how are they related? Br J Psychiatry. 1988;152:629–31.
135. Snyder DK, Berg P. Determinants of sexual dissatisfaction in sexually distressed couples. Arch Sex Behav. 1983;12(3):237–46.
136. Barnas J, Parker M, Guhring P, Mulhall JP. The utility of tamsulosin in the management of orgasm-associated pain: a pilot analysis. Eur Urol. 2005;47(3):361–5. discussion 5.
137. Johnson CW, Bingham JB, Goluboff ET, Fisch H. Transurethral resection of the ejaculatory ducts for treating ejaculatory symptoms. BJU Int. 2005;95(1):117–9.
138. Antolak S, Hough D, Maus T. Chronic pelvic pain syndrome (pudendal neuralgia or category

IIIB chronic prostatitis). Rochester, MN: Mayo Clinic; 2002.
139. Kulik FA, Wilbur R. Case report of painful ejaculation as a side effect of amoxapine. Am J Psychiatry. 1982;139(2):234–5.
140. Aizenberg D, Zemishlany Z, Hermesh H, Karp L, Weizman A. Painful ejaculation associated with antidepressants in four patients. J Clin Psychiatry. 1991;52(11):461–3.
141. Hsu JH, Shen WW. Male sexual side effects associated with antidepressants: a descriptive clinical study of 32 patients. Int J Psychiatry Med. 1995;25(2):191–201.
142. Michael A. Venlafaxine-induced painful ejaculation. Br J Psychiatry. 2000;177:282.
143. Demyttenaere K, Huygens R. Painful ejaculation and urinary hesitancy in association with antidepressant therapy: relief with tamsulosin. Eur Neuropsychopharmacol. 2002;12(4):337–41.
144. Roberts RO, Jacobson DJ, Girman CJ, Rhodes T, Lieber MM, Jacobsen SJ. Prevalence of prostatitis-like symptoms in a community based cohort of older men. J Urol. 2002;168(6):2467–71.
145. Nickel JC, Downey J, Hunter D, Clark J. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. J Urol. 2001; 165(3):842–5.
146. Litwin MS, McNaughton-Collins M, Fowler Jr FJ, Nickel JC, Calhoun EA, Pontari MA, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol. 1999;162(2):369–75.
147. Amarenco G, Ismael SS, Bayle B, Denys P, Kerdraon J. Electrophysiological analysis of pudendal neuropathy following traction. Muscle Nerve. 2001; 24(1):116–9.
148. Nadler RB, Rubenstein JN. Laparoscopic excision of a seminal vesicle for the chronic pelvic pain syndrome. J Urol. 2001;166(6):2293–4.
149. Anderson RU, Wise D, Sawyer T, Chan CA. Sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: improvement after trigger point release and paradoxical relaxation training. J Urol. 2006;176(4 Pt 1):1534–8. discussion 8–9.

Optimizing Research in Erectile Dysfunction

26

Yvonne Y. Chan, Rafael G. Gonzalez, and Alan W. Shindel

Introduction

Erectile dysfunction (ED) is defined by the NIH as "the inability to attain and/or maintain an erection sufficient to permit satisfactory sexual intercourse" [1]. ED is a common disease state that affects many men; its prevalence increases with age. In a 2007 study on sexual health in the USA, 87.3 % of men aged 57–64 years were sexually active. However, the number of men aged 75–95 years who were sexually active was much lower at 38.5 % [2]. ED is associated with multiple risk factors including age, hypertension, diabetes, hyperlipidemia, smoking, polypharmacy, and obesity. There has been a great deal of interest in ED as a marker for early subclinical cardiovascular disease in young men [3, 4].

Given the importance of sexuality in human relationships, ED has been a topic of intense research interest. This complex disease can be studied at the biological, psychosocial, and epidemiological levels. In this chapter, we explore characteristics of quality research in general with particular focus on the current state of the art in ED research. We will also propose important avenues in advancing the field of ED from biological, psychological, and epidemiological perspectives.

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General Principles of Research

Research has become the basis and guide of modern medicine. Within the last century, physicians have witnessed a paradigm shift in medical practice and education with the introduction of evidenced based medicine (EBM). Rather than basing clinical decisions solely on prior training, intuition, and personal experiences, medical practitioners have been encouraged to identify questions regarding patient care, gather relevant literature, and critically evaluate the data to guide management [5]. This practice is highly contingent on the availability of quality studies. Clinical judgment, experience, and intuition will remain important components in the practice of clinical medicine when determining how to apply EBM to individual patients and when robust EBM guidelines are not available.

Study Design

EBM is based on the publication of sound science. The foundation of the scientific method (and by extension every scientific study) is the formulation of a clear and testable research hypothesis. A well-

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formulated hypothesis details the study target, the intervention or exposure being evaluated, and the outcomes that will be examined [6]. Once the hypothesis is generated, the researcher can select an appropriate study design which will either support or disprove the hypothesis. Typically this involves selecting a "main outcome measure" that will be the focus of data collection. Broadly speaking, studies may be divided into qualitative and quantitative designs. Research that involves both qualitative and quantitative elements is sometimes referred to as "mixed methods" [6].

Qualitative Research

Qualitative research is designed to gather information on behaviors and thoughts on individuals [7]. This research method relies heavily on interviews and in some cases small group discussions. These sessions are facilitated by an experienced interviewer who will in most cases adhere to a template of questions; these questions are a starting point for conversation with the participant(s). While the template is a starting point, qualitative research relies on questions that are open-ended and will allow the participant(s) to articulate their personal views and feelings. This approach is often times called "semi-structured interviewing," providing a rough framework to keep the conversation on point but permitting the subject to express themselves freely [6, 7].

Qualitative research is used widely in the preliminary phases of large scale quantitative research. It also plays an important stand-alone role in gathering information and opinions on topics of interest, particularly in specific populations that may be excluded from larger epidemiological/clinical studies [7].

Quantitative Research

Quantitative research emphasizes objective evaluation of numerical data. This type of research may be further subdivided into observational and experimental designs [6]. Observational studies are widely employed in epidemiological research and can be further subdivided into cross-sectional, cohort, or case-controlled studies [8].

In cross-sectional research, individuals are surveyed at one particular time point regarding their exposure to the phenomena of interest and the outcome measured; typically a number of other factors are also assessed to reduce the likelihood of spurious findings from confounding factors [9]. Cross-sectional studies are useful for determining prevalence and studying associations between variables of interest.

Cohort studies follow a specific group over time and compare the incidences of the outcome of interest between the exposed and non-exposed groups [10]. This study design is more costly and time intensive than cross-sectional studies. However, longitudinal cohorts are useful in determining incidence rates and establishing natural progression and associations over time.

Case–control studies compare two groups selected based on the presence or absence of an exposure or parameter [10]. After groupings are made, differences between individuals who have and do not have the condition of interest can be elucidated, providing useful association data. This is perhaps the most "experimental" of the observational study designs with the caveat that the researcher has no control over the exposure. The case–control design is helpful to study diseases that are relatively rare [11].

The principle limitation of observational studies is their limited ability to establish causality as opposed to simple association [12]. Experimental studies, if well designed and executed, may provide the best quality data on actual causal factors for conditions of interest. In these studies, subjects are randomized into two or more groups and subjected to different interventions in a controlled manner [13]. Experimental studies are limited by the inherent expense in design and execution. While randomized, double blinded, placebo controlled trials are often held up as the highest level of evidence, a poorly designed experimental study may not be as valuable as a well-designed observational study.

Choosing the appropriate study design will maximize the ability to support or disprove the hypothesis. The quality of study design (regardless of type) is highly dependent on internal, external, and statistical validity (Table 26.1).

Table 26.1 Internal, external, and statistical validity

Internal validity	External validity	Statistical validity
Definition		
• Determines how well the manipulation of the independent variable (IV) caused the change in the dependent variable (DV) (i.e. causal relationship)	• Measure how well the cause–effect relationship from an experimental study can be replicated and applied to the general population	• Determines if the observed relationship was a result of a cause–effect relationship between independent and dependent variables or by pure chance
Threats		
• *History*: The time that passes by during the experiment can influence the final outcome • *Maturation*: Study participants will mature or change during the experiment, and that will influence the final outcome • *Regression*: Participants with extreme scores will regress to the mean	• *Selection and treatment*: Study outcomes cannot be generalized to populations that do not have the same characteristics as the study population • *Setting and treatment*: Study outcomes cannot be generalized to populations outside of the setting characteristics of the study • *History and treatment*: Outcomes cannot be attributed to past events or generalized to future events	• *Low statistical power*: Can increase the chance of committing type II error • *Test assumptions*: Implies that the data are adequate to test a specific cause–effect hypothesis • *Heterogeneity*: Greater variability of the study participants will increase the variance of the cause–effect relationship • *Internal validity threats*: Any threat to interval validity will impact the overall statistical conclusions of the study

Internal Validity

Internal validity is the term used to describe how well the main outcome measure(s) accurately assess the phenomenon under study [14]. For example, the International Index of Erectile Function (IIEF) has been established as a simple quantitative metric that accurately measures the presence and severity of ED from a variety of different causes in a variety of different populations of men [15]. The broad internal validity of this scale for assessment of erectile function has made the IIEF the most commonly used clinical metric for ED assessment in clinical research and practice. In making the diagnosis of ED, the IIEF has superior internal validity when compared to binary response (yes/no) questions on evaluating for the presence of sexual dysfunction and permits a more nuanced, quantitative measure [15].

In the field of erectile dysfunction research, internal validity may be affected by factors such as the methods used to measure erectile responses in animal models, the definition of ED in human studies, use and applicability of measurement tools for ED, study duration, drug dosage, and study completion rates [16, 17].

External Validity

External validity is the degree to which the measured outcomes are applicable to the general population [18]. This is influenced by characteristics of the study population which is defined by the inclusion and exclusion criteria as well as the method of patient accruement. Accrual of a very large group of study participants does not necessarily make a study externally valid; if the study group is not reflective of the larger population of interest (due to disparities in race, socioeconomic status, etiology of ED, medical comorbidities, etc.), the results cannot necessarily be extrapolated to the overall population; rather, the results may only apply to the population that is similar to the limited subset that was enrolled.

For studies on erectile dysfunction, external validity may be affected by use of human versus

animal tissues in basic science studies, the etiology of ED in clinical studies, cultural and demographic factors, and patient co-morbidities [17].

Statistical Validity

Statistical analysis is based on assessment of probabilities rather than definitive statements of fact. A hallmark of science is that while hypotheses may be rejected, no hypothesis can ever be completely proven with 100 % certainty [6]. In practice, scientists and researchers rely on statistics to provide an estimate for the likelihood that a relationship is present between variables under study. The familiar "*p* value" is a percentage estimate of the chance that an observation is due to chance alone. It is most common to accept that a *p* value of <0.05 as indicative of a significant and real difference between groups; in this situation the chances that an observed difference between groups is due to chance alone is 5 % or less. This level of certainty is generally agreed upon as an acceptable margin for error and most findings with $p<0.05$ are accepted as likely true and statistically significant [19].

Because science is based on probability, it must be borne in mind that accepting a *p* value of 5 % or less indicates that approximately 1 in 20 studies will report a "significant" finding that is due to chance alone. Stating that a relationship is present when in fact there is none is called a Type I (or false positive) error. A related possibility is that a study may fail to detect a relationship between variables when there is indeed a relationship. This is known as a type II (or false negative) error [20].

Because there is an inherent possibility of Type I and II error in science, another critical pillar of scientific research is replication. A single study, no matter how well designed, may be in error. However, it is very unlikely that numerous studies will report the same outcome unless a true relationship is present. The need for replication is the foundation for meta-analyses, a research process in which studies on a related topic are combined in order to produce a larger and more externally valid study group. Well-designed meta-analyses of quality studies are important tools for establishing EBM practices and guidelines for science and medicine [20].

Statistical power is a critical concept and is related to external validity. Briefly, a study's power determines whether or not the sample size in a study is sufficient to answer the research question. Because power analysis is designed to answer a research question it must include a clear statement of the testable, quantifiable hypothesis. In most cases there is also a "null hypothesis" which states that there is no difference between two groups under study [21]. The researchers must establish the expected difference between the study populations and also determine the acceptable likelihood of a type I or II error. It is standard practice to accept a 5 % risk of type I error and a 20 % risk of type II error although these parameters are subject to modification depending on the nature of the research in question [20]. Finally, it is also important to establish what statistical difference is clinically/scientifically relevant.

Caution must be exercised when interpreting data from research that does not include a carefully detailed power analysis conducted before study initiation. A "post hoc" analysis (done after data collection is completed) is suboptimal as well. Studies with small populations are at risk of being underpowered and hence not of sufficient size to detect meaningful differences. Conversely, studies with very large populations may be overpowered; inclusion of very large groups in a study may lead to statistically significant but clinically meaningless differences between groups. Overpowered studies may be used to justify conclusions that are not well supported [20].

Optimizing internal, external, and statistical validity produces quality research that adds to our scientific knowledge and improves patient care. To optimize the quality of ED research we must evaluate the current state of our understanding and design future research in line with sound scientific principles; this fundamental principle applies to all types of ED research, including bench research, qualitative interviews, clinical trials, and epidemiological surveys.

Basic Science Studies in ED

The etiology of ED is multifactorial and includes psychogenic, neurogenic, vascular, and hormonal components. Of these various factors, vascular causes of ED are of particular interest as regulation of blood flow to and from the penis is generally the common final pathway of penile erection [22]. While vascular status is the final arbiter of erections, basic science research on hormonal and neuronal modulators of erectile function is also of great interest. Studies involving cell cultures, organ baths, and animal models have offered great insight into these often intertwined and complex pathways and have enabled better understanding of ED pathophysiology and novel treatments.

Cell Cultures and Organ Baths

Cell cultures of penile cavernosal smooth muscle cells and endothelial cells provide controlled environments to study the molecular factors and cellular receptors involved in the regulation of penile vasculature. Ex vivo studies of rat cavernous smooth muscle cells have demonstrated that VEGF and IGF-1 secretions varied by age and correlated with smooth muscle cell migration [23, 24]. This in turn has led to similar studies in human penile cavernosal smooth muscle cells which demonstrated the prevalence of two splice variants of VEGF and its receptor Flt-1. The study showed that exposure to VEGF results in a two- to threefold increase in human penile cavernosal smooth muscle cells [25]. Further studies in human endothelial cells have teased out the effects of VEGF on endothelial production of nitric oxide, a major molecular messenger critical to erectile function [26]. Cell culture studies have therefore offered greater insight into the molecular and signal transduction pathways involved in penile erection and how such pathways are affected in diseased states such as chronic ischemia [27], vascular insufficiency [28], or hyperglycemia [29].

These in vitro studies have provided molecular targets for future studies on the effects of angiogenesis in erectile dysfunction. However, cellular studies are limited by their ex vivo nature and the non-physiological conditions in which they are conducted. For example, most studies are based on monocultures of cavernous endothelial or smooth muscle cells which limit their representation of in vivo states (i.e., decreased external validity). A co-culture system of cavernous endothelia and smooth muscle cells has been developed and may partially offset this limitation [30].

While cell cultures offer a molecular understanding of erectile dysfunction, organ baths have allowed researchers to further evaluate how such molecular changes affect smooth muscle biology at the tissue level, especially in diseased states. For example, obesity is a known risk factor for ED. Organ baths of corpus cavernosal tissue from mice fed with a high fat diet or the standard diet were utilize to study penile effects of obesity, an increasingly prevalent human problem. Functional responses of the tissue to electrical field stimulation, endothelium dependent, and endothelium independent agents were evaluated. Tissues from obese rats had diminished relaxation and increased contractility in response to electrical field stimulation and phenylephrine, respectively. Cellular cGMP levels were lower in the experimental group. Collectively, these data suggest that obesity may affect endothelium dependent vasoreactivity, increasing the risk of erectile dysfunction in humans [31].

Not only do organ bath studies help translate the effects of molecular pathways to structural changes, they also offer a medium to evaluate drug therapy. For example, the synergistic relaxant effect of the phosophodiesterase type 5 inhibitor (PDE5I) sildenafil and the alpha blocker doxazosin on cavernosal strips was explored using organ bath methodology [32]. Like cell cultures, organ baths are limited by their ex vivo study conditions but offer a medium through which the connections between molecular pathways and structural tissue changes may be studied.

Human Biopsy Specimens and Cadavers

Human biopsy or surgical specimens for patients with ED have revealed structural and molecular changes that contribute to the disease process.

In an analysis of the penile corpora cavernosa of patients with severe ED and men without urogenital conditions, researchers compared biopsy specimens taken from men undergoing inflatable penile prosthesis implantation to fragments of corpora cavernosa from autopsies of men who died of other causes. They revealed a statistically significant reduction in elastic fibers in the ED group but no significant differences in the presence of collagen or smooth muscle fibers [33]. In another recent study, researchers compared surgical specimens of patients who underwent open retropubic radical prostatectomy versus robot-assisted radical prostatectomy. These specimens were stained with neuronal nitric oxide synthase (nNOS) antibodies. The patients who underwent the open procedure with nerve sparing were found to have a significantly high number of nNOS positive nerves which correlated with worsened erectile dysfunction, suggesting (albeit not definitely determining) that the robotic assisted procedure may be more precise in preservation of the neurovascular bundles. This study suggests that nNOS staining of prostate specimens after prostatectomy may be helpful in predicting postoperative erectile dysfunction [34]. Follow up assessment of erectile responses in these men is necessary to establish the clinical validity of these suppositions.

Human cadavers have offered insight into structural components that contribute to ED. In these studies, factors such as hormonal deficiency, arterial insufficiency, psychosocial effects, and drug effects are inconsequential. Under such conditions, researchers can focus on aspects of the human anatomy that may predispose to erectile dysfunction should this anatomy be disrupted by pelvic surgery or the penile blood supplies be interrupted by atherosclerotic disease. For example, a 2002 study evaluated 120 human cadaveric penile specimens. Transverse sections were obtained at the level of the pubic bone, mid penile shaft, and at the sulcus coronaries. Atherosclerotic stenosis was found in 65 % of the specimens of which 20.4 % occurred proximally, 37.1 % centrally, and 42.5 % distally. This observation helped explain the poor results seen from revascularization surgery, suggesting that only patients with solitary vascular lesions are likely to benefit from penile revascularization for ED [35]. Further studies that couple human cadaveric histology with advances in computer technology have provided detailed maps of penile arterial anatomy. For example, a 2013 study evaluating penile specimens from five human cadavers used immunolabeled serial 2D sections as the basis for computer generated 3D anatomical reconstructions. This revealed anastomoses between the dorsal, cavernous, bulbo-urethral, and urethral arteries which may provide collateral blood flow to the corporal cavernosa after radical prostatectomy and potentially aid in recovery of erectile function [36]. Given the wide variability in human anatomy, cadaveric studies have provided insight into the intricacies of penile anatomy, though the application of such knowledge to surgical therapy warrants further research.

Animal Models

Early studies of ED in the 1960–1990s utilized large animal models including dogs, monkeys, cats, and rabbits and provided the foundation for our current understanding of erectile hemodynamics [37]. Through studies in the monkey and canine models, Lue et al. demonstrated that penile tumescence was the result of active relaxation of sinusoidal spaces, arterial dilation, and venous occlusion [38, 39]. Carati et al. evaluated the role of sympathetic innervations on erectile function in anesthetized dogs [40]. Mating behaviors in these larger animals are more easily quantifiable as mating occurs over a longer time frame compared to that in rats and mice. Furthermore, the sizes of these animals enable researchers to study multiple endpoints as there are more vascular and erectile tissue samples available. Nonhuman primates, in particular, carry the unique advantage in that they are most similar to human beings with regard to sexual behavior and physiology. Progression of vascular disease caused by high cholesterol diets also simulate that of human beings, making results from such studies more applicable to their human counterparts.

However, these large models are generally expensive to support and there are few facilities available to house them. Their lifespan is also longer than that of mice, making support time consuming [22]. Furthermore, there has also been a recent push towards minimizing the use of non-human primates in research [41]. These factors have generally limited their use in contemporary studies although they do represent the most externally valid animal model of human penile erection.

In recent years, large animal models and non-human primates have generally been replaced by the rat and mice models. The rat model has been utilized in multiple studies and carries the advantages of small size, low cost of use, and well-defined models for evaluating ED. Erections may be induced in rats by administering apomorphine, electrical stimulation of the cavernous nerves, or penile administration of vasoactive agents (e.g., prostaglandin E1, papavarine). Erectile function may be assessed by recording intracavernosal pressure on conscious or anesthetized animals [22]. The rat model has helped elucidate the roles of various pathways integral in the pathophysiology and treatment of ED including that of nitric oxide and RhoA/Rho-kinase [42, 43]. Certain rat models including the Zucker obese/diabetic rats and the Brown-Norway model enable researchers to simulate the effects of diabetes and aging on erectile function. Such studies have helped elucidate the roles of protein kinase C and Rho-kinase in facilitating the vasoconstriction state of the penile smooth muscle in obesity [44] as well as the effects of age related alterations in VEGF mRNA expression [45]. They are also the study targets of gene therapy. Researchers have shown that transfection of diabetic Sprague Dawley male rates with adenoviruses containing protein kinase G1α restored PKG1 activity and improved erectile function in the experimental group compared to control [46]. Despite their contributions to molecular, cellular, and therapeutic studies of erectile dysfunction, however, rat models remain limited in differences in their mating behaviors and overall lifespan. Furthermore, their life span ranges from 1 to 3 years, which is relatively short compared to that of humans [22].

Similar to the rat, the mouse model for study of penile hemodynamics is inexpensive albeit somewhat harder to work with given smaller size. Mouse models are more easily subjected to genetic manipulation with gene knockouts (i.e., inactivation of genes of interest) [22]. For example, studies on mutant mice with knockouts of neuronal nitric oxide synthase (NOS) or endothelial NOS have identified splice variants of neuronal NOS as potential mediators of erectile function and as such, potential therapeutic targets [47]. Some studies have evaluated further downstream targets of the nitric oxide pathway including the calcium activated potassium channel (BK_{Ca}). It was demonstrated that treatment dose sildenafil had decreased efficacy in these BK_{Ca} knockout mice, suggesting that this potassium channel is important in the action of sildenafil in vivo [48]. These genetic studies offer more direct evidence of the molecular effects of certain targets on ED and may lead to future therapies.

Future Drug Targets

The knowledge we have gained from cell cultures, organ baths, and animal models have led to various potential forms of medical therapy. The most widely used are the phosphodiesterase 5 inhibitors. PDE5I promote cyclic GMP (cGMP) accumulation in patients with erectile dysfunction by inhibiting its degradation. The efficacy of PDE5I, however, is blunted in patients who are deficient in nitric oxide, including men with diabetes, nerve trauma from pelvic surgery, or advanced age [49]. For these patients, soluble guanylate cyclase activators are promising forms of drug therapy that produce cGMP by direction activation of guanylate cyclase without the requirement for nitric oxide. YC-1 is a direct soluble guanylate cyclase activator that operates through an allosteric binding site and has been shown to facilitate erectile function in rats [50]. Intracavernous YC-1 injections into rat corpus cavernosa produced erectile responses and dose dependent increases in intracavernous pressures [51]. Another soluble guanylate cyclase activator, BAY 60-4552, was found to be effective in

increasing erectile response in rats with bilateral cavernous nerve crush injuries. Male adult Sprague-Dawley rats with bilateral cavernous nerve crush injuries were treated with vardenafil, BAY 60-4552, or the combination of the two drugs and the combination treatment restored erectile responses to that of the control with erectile stimulation. This suggests a synergistic effect of the two drugs and the potential benefit for combination therapy in patients with post-radical prostatectomy ED [49]. To date, the effects of YC-1 and BAY60-4552 in men with ED have not been published in the peer-reviewed literature.

While still in the preclinical stages, Rho-kinase inhibitors are also potential therapeutic agents of interest. Previous studies have revealed that binding of norepinephrine, angiotensin II, or endothelin-1 to G-protein coupled receptors led to the conversion of RhoA-GDP to RhoA-GTP. The latter migrates to the cytoplasmic membrane and activates Rho kinase (ROCK) which phosphorylates and inactivates myosin light chain phosphatase, thereby maintaining cavernous smooth muscle contraction [52, 53]. Hannan et al. treated Sprague Dawley rats with bilateral cavernous nerve injuries with Y-27632, a ROCK inhibitor, twice daily for 2 weeks. The authors reported that treatment group had fewer apoptotic cells, decreased ROCK activity, higher nitric oxide synthase levels, and improved erectile responses to cavernous nerve stimulation [54]. This may suggest a role of ROCK inhibition in post-prostatectomy erectile dysfunction. ROCK inhibition with another agent, fasudil, has also been shown to improve erectile function in diabetic rats, suggesting its potential use in neurogenic diabetic erectile dysfunction [55]. SAR407899A, a potent and selective ROCK inhibitor, has been studied in a clinical phase II trial of 20 men with mild to moderate ED. The study was completed in 2009 but results are not yet published [52].

In summary, basic science studies have provided a step-wise approach to the understanding of ED. Cell cultures have clarified major molecular signaling pathways involved in ED. The effects of these pathways on penile structural changes were then further elucidated in organ baths and animal models, yielding potential therapeutic targets and paving the paths for ED therapy.

Clinical Studies in ED

Medical therapy for ED is of great interest. Of the various available drug therapies, PDE5I are the mainstay and first line agents of choice for ED of virtually every etiology [56]. The vast majority of studies on clinical pharmacotherapy for ED have focused on PDE5I.

PDE5I competitively bind to Phosphodiesterase type 5 (PDE5), an enzyme which is responsible for degrading the cellular second messenger cGMP to 5-prime GMP. cGMP is the mediator of numerous cellular processes that lead to vasodilation and hence plays an important role in promoting penile erection. Inhibition of PDE5 has the effect of increasing intracellular concentrations of cGMP, leading to relaxation of the smooth muscle cells of the corpus cavernosum. PDE5I such as sildenafil, tadalafil, vardenafil, and avanafil are recommended as initial therapy for ED based on proven efficacy and safety from numerous trials [57].

The utilization of PDE5I as prophylactic agents for prevention or reversal of ED has been of great interest as studies have yielded inconsistent results. Animal studies and several small non-randomized studies of penile rehabilitation (e.g., administration of routine dose PDE5I after prostatectomy) suggested improved erectile function over time [58–60]. However, larger, randomized, and placebo-controlled trials failed to show any sustained benefit in terms of spontaneous erectile function after routine dose PDE5I after prostatectomy [61, 62]. A recent randomized, prospective study of 279 patients with localized prostate cancer treated with radiation evaluated the use of prophylactic sildenafil on erectile function and patient satisfaction. Using IIEF as a metric to evaluate erectile function and RAND SF-36 to evaluate quality of life, the authors showed that daily sildenafil dosage was associated with improved overall satisfaction scores and IIEF scores at 12 months [63]. A similar study evaluating the efficacy of tadalafil

as a preventive agent, however, showed no benefit. This study similarly used IIEF as a metric for erectile function but evaluated sexual and marital satisfaction using the Sexual Adjustment Questionnaire and Locke Marital Adjustment Test [64].

The search for novel drug therapies remains a great focus of current clinical studies in erectile dysfunction. Second generation PDE5 inhibitors including udenafil and mirodenafil have been launched in South Korea after evaluation in several double blind, placebo controlled, and randomized controlled trials [52, 65, 66]. The study of udenafil in young, healthy South Korean men showed that the drug is generally well tolerated with minimal side effects of facial flushing, impairment of color discrimination, and nasal stuffiness [65]. Evaluation of mirodenafil showed increase in IIEF Q3 and Q4 scores in the treatment group compared with the control group [66]. While these studies are instrumental in establishing the safety profile and efficacy of these potentially new forms of therapy, studies on the safety and side effect profiles of this drug in other populations will be of great interest. When establishing the safety profile of udenafil, healthy South Korean volunteers aged 19–32 were studied, limiting one's ability to apply the data to populations such as the multiracial, elderly population of the USA. The mirodenafil study excluded men with spinal cord injury, history of radical prostatectomy, psychiatric disease, coronary artery disease, and those with penile anatomical abnormalities, limiting our ability to apply the study data to these populations, many of whom are the ones who will eventually be prescribed these medications by practitioners. These efforts will be an extension of the external validity of the studies.

Epidemiological Studies in ED

Erectile dysfunction affects men of all ethnicities and backgrounds but is also more common among men with cardiovascular diseases and the Metabolic Syndrome [67]. Its prevalence in these patient populations and its role as a subclinical marker for these conditions have been areas of increasing study. Furthermore, the prevalence and associations of ED in populations that have not been the subject of ED research are areas of increasing attention.

Erectile Dysfunction and Chronic Medical Problems

ED is common among men with type 2 diabetes and addressing this aspect of their health has been emphasized in recent studies [68]. An observational study of 220 men followed for type 2 diabetes at a single center in Italy showed that 52.9 % of the patients had erectile dysfunction and the prevalence of ED increased with the number of times these men's hemoglobin A1c were greater than 7 % [69]. A survey of 3991 men whose data were present in the National Health and Nutrition Examination Survey from 2001 to 2002 and 2003 to 2004 showed that patients with fasting blood glucose between 100 and 126 mg/dL and greater than 126 mg/dL had higher odds of ED (OR 1.22 [CI, 0.83–1.80] and 2.68 [CI 1.48–4.86] respectively). Similarly, patients with hemoglobin A1C greater than 6.5 % had an odds ratio of ED of 3.70 (CI 2.19–6.27) [70]. These studies have established a strong correlation between metabolic disease and ED, which may provide strong incentives for men with these conditions to implement lifestyle changes.

Not only is ED prevalent in men with diabetes, it may be a marker of sub-clinical cardiovascular disease. Evaluation of 192 patients with ED revealed high blood pressures and insulin resistance index, suggesting that this may be one of the early clinical signs of endothelial dysfunction that occurs in metabolic diseases [71]. In a longitudinal cohort study of 965 men without diagnosed cardiovascular disease, researchers demonstrated that persistent ED was associated with increased Framingham cardiovascular risk, especially in men less than 50 years of age [3]. A meta-analysis of seven cohort studies also demonstrated that the relative risk for cardiovascular disease for patients with ED was 1.41 (95 % CI, 1.22–1.64) [72]. In a 2015 cost analysis, Pastuszak et al. estimates that if men with ED were screened for cardiovascular disease, 5.8 million men with unrecognized

cardiovascular risk factors may be identified over 20 years. With screening and intervention, approximately 1.1 million cardiovascular events may be avoided which can save up to 21.3 billion dollars [73]. These studies implicate the role of erectile dysfunction as an early marker that may eventually prompt general practitioners to evaluate and treat previously unrecognized underlying cardiovascular risk factors.

ED in Men Who Have Sex with Men

Little is known about sexual dysfunction in men who have sex with men (MSM) but there has been increasing research in this population. In a 2009 study, 79 % of 7001 MSM recruited from internet social networking, chat, and news websites reported the presence of low sexual desire, erection problems, and performance anxieties [74]. In a 2012 internet survey based study of 2640 men, researchers found that increasing age, HIV seropositivity, and lack of a stable sexual partner were associated with greater odds of ED [75]. These risk factors were similarly demonstrated in another internet based survey of Belgian MSM which showed that having a steady partner offered an odds ratio of 0.59 ($p<0.001$) whereas increasing age had a OR of 1.04 ($p<0.0001$) [76]. A majority of these studies are internet based. The anonymity may enable respondents to answer more sensitive questions than in person interviews. However, this medium limits the study population to men with internet access; questions also remain about other factors relevant to the external validity of anonymous internet based surveys.

Qualitative Studies in ED

Gathering information from patients and/or their partners on feelings relating to ED and treatment are essential to guiding successful clinical interactions. While quantitative data supply important information on efficacy, qualitative data help clinicians understand patient perspectives and narratives about their condition. This may be useful to help build empathy and better counsel men and their partners about their condition. One example of the utility of qualitative research was a recent study by Carvalheira et al. which studied the reasons for discontinuation of PDE5I therapy in men with ED. The most frequent reasons for discontinuation included lack of efficacy, psychological issues, and concerns about safety profile [77]. PDE5I discontinuation is common; studies such as this help providers to understand why failures occur; this may help to facilitate salvage of therapy or more rapid progression to alternative treatments.

Qualitative methods have also been used to study the feelings and thoughts of female partners of men with ED. McCabe et al. reported on the feelings and thoughts of women whose male partners were treated for ED with a PDE5I. In this study the female participants reported a number of benefits post-treatment, including better communication and emotional intimacy [78].

Qualitative research may also help researchers better understand the perspectives of specific sub-populations of men dealing with ED. For example, a recent qualitative study on the experience of gay men with prostate cancer revealed interesting data on how gay couples may adapt to treatment related ED. Many of the themes of loss and frustration were present but the researchers were able to identify some novel adaptive practices that had not to date been extensively documented [79].

Optimizing Future Research

Fundamentally, what is most important to optimize future research in ED is to adhere closely to the fundamentals of research articulated above. Adherence to principles of research must be tempered by the real world issues of limited resources in terms of money, time, and institutional/societal support. “Perfect” studies are an unobtainable goal but researchers and clinicians should of course strive to control for limitations when possible and to acknowledge them when they are unavoidable.

Optimizing Basic Science Research

Basic science research is where paradigm shifts and completely novel treatments begin [80]. Without basic science research, none of the pharmacotherapies that form the mainstay of ED management would be available. Hence, commitment to research on the physiology of erections and pathophysiology of ED remains essential [81].

We have a thorough understanding of how the penis becomes erect at both the molecular and tissue levels. That said, an enhanced understanding of the various molecular messengers that mediate vasodilation will likely improve our understanding of how ED happens and present targets for future therapies [82].

When a promising molecular target is identified, it is necessary to determine if it is amenable to pharmaceutical intervention. Generally either suppression (in the case of molecules that oppose genitovasodilation) or activation (in the case of molecules that enhance vasodilation) are the interventions of choice. High throughput screening and computed aided molecular modeling techniques (sometimes known as in silico studies) may enable intelligent drug design to expedite the drug discovery process [83, 84]. This software may also help predict in advance which compounds are likely to be bioavailable and/or toxic. It is desirable that this sort of processing occur prior to additional steps in drug development as even animal studies incur substantial expense; it is ideal to screen out drugs that are unlikely to be clinically useful as early as possible [84, 85].

Computer programs are useful for high throughput screening but limitations of our knowledge and the markedly higher complexity of living tissue means that studies on tissues and whole organisms will remain essential [84]. Cell cultures, organ bath studies, and other studies involving cells and tissues from living organisms serves as an intermediary step between in silico and in vivo research. Research of this nature may yield important information on physiology, pharmacology, and real-world activity of agents under study for management of ED [32].

Pharmaceutical management of ED remains the mainstay of clinical management at this time; however, there has been long-standing interest in restorative therapies that would obviate the need for on demand therapies [86–89]. Stem cells, gene therapy, and trophic cytokines have all been advanced as modalities that may restore natural penile erection. Use of cytokines and gene therapies are generally based on known pathophysiological processes that are potentially amenable to manipulation of cellular milieu and/or local gene expression, respectively. Stem cells have long been thought to act by differentiation and replacement of diseased cells and tissues, although an increasing body of evidence seems to indicate that cytokine release is a more likely mediator [90, 91]. While initial results have been promising long-term studies on safety and durability of treatment response are essential.

Animal testing has been a mainstay of basic science research for centuries. It is likely that it will continue to play an important role [92]. However, serious concerns have been voiced about species-specific differences in physiology that may limit the applicability of findings in non-human animals (i.e., limited external validity of animal models for erectile physiology and ED) [22, 93, 94]. Furthermore, changing social mores have increased pressure on researchers to limit the use of animals in research and to adhere to the highest possible standards of humane treatment. This includes limiting the number of animal used in research, providing comfort measures for animals subjected to procedures, and using euthanasia methods that minimize animal suffering both physically and (as best we are able to determine) psychologically [41].

Optimizing Clinical Research

A key limitation of clinical research is study group. It is well known that some populations (e.g. racial minorities, sexual minorities, socioeconomically disadvantaged persons) are less represented in research and as such are less likely to benefit from the eventual findings of said research [95, 96]. Recent studies suggest that this may not necessarily be due to lack of willingness

in these study populations, which has been a commonly held belief [97, 98]. This poses a significant problem in terms of the external validity of research findings. Hence, a critical consideration for future clinical ED research is enrollment of study populations that are reflective of the larger population under study. There may still be a place for focused studies on specific populations but such studies must be acknowledged as reflective of observations in only a select sub-set of the larger community [99].

Before enrollment even begins on a clinical trial for ED, the researchers should lay the groundwork for study parameters as detailed above. Of particular importance is a clear statement of a primary research hypothesis; all of the subsequent study design should be geared towards answering this single, refutable research question. Many published papers leave the hypothesis vague, stating that the desire is to "explore relationships" or "investigate a certain population." While these may be reasonable goals, without a testable hypothesis that is amenable to being rejected a truly rigorous scientific study cannot occur [100]. In a similar vein, without statement of hypothesis, it is difficult or even impossible to perform a power calculation; without a power calculation the reader (and the researcher for that matter) cannot possibly know whether the sample size was appropriate, neither too large (in which case spurious and clinically insignificant differences can be amplified into statistical significance) nor too small (in which case potentially important differences may be missed for lack of adequate sampling) [101]. It is highly advisable that researchers who do not have a strong background in statistical methods enlist the aid of a qualified statistician early in the process of trial design.

Utilization of validated endpoints remains critical [102]. A salient case in point is older studies on ED after radical prostatectomy. These studies often relied on simple patient report (binary of "yes" or "no") to determine presence or absence of ED. A respondent might report that he was able to engage in intercourse and hence be coded as not having ED; what was not necessarily taken into account was increased difficulty engaging in penetrative intercourse in men who had previously had no difficulty, decreased erectile rigidity leading to lower satisfaction for the man and his partner, and a higher prevalence of sexual encounters during which the erection did not attain and/or maintain sufficient rigidity [103, 104]. It must also be considered that many patients typically wish to provide the "socially desirable" response when directly questioned and hence many men may deny the presence of ED even when it is present [1].

It is preferable to use validated instruments such as the International Index of Erectile Function (IIEF) or related scales to quantify degree of erectile and change over time [15, 105]. These metrics typically report continuous data that permit a more nuanced assessment of changes in sexual function over time or after treatment. While continuous variables are nuanced there remains a place for categorical assessments of erectile response; a commonly utilized binary response option are the Sexual Encounter Profile (SEP) questions, particularly question 2 (which deals with attaining an erection sufficient for penetration) and 3 (which deals with maintaining an erection sufficient for penetration [106].

Finally, the research study should be controlled to account for confounding variables. Health, demographic, and psychosocial factors that contribute to ED should be elicited and appropriate statistical analysis conducted so as to minimize the interference from these other variables [68, 107].

Optimizing Epidemiological Research

Concerns about the external validity that apply to clinical research are also highly relevant, perhaps even more so, in epidemiological research [108].

In the past, epidemiological research relied on mail and/or telephone contact. The advent of the internet and electronic mail (e-mail) has revolutionized the practice of epidemiological research but introduced new limitations [109]. It is very easy for researchers to contact large groups of people with relative ease; by selection of interest groups and/or tailoring of invitations researchers may rapidly and cheaply accrue large study

Table 26.2 Suggestions for future directions in ED research

	Current	Future
Basic science research	• Effects of molecular agents on cultures of cavernosal smooth muscle cells or endothelial cells • Human cadaveric studies on penile anatomy • Simulation of diseased states in animal models (dogs, mice, rats, nonhuman primates) to study the pathophysiology of ED and the effects of drug therapy	• Optimization of coculture systems to study the combined effects of molecular agents on both cell types and their interactions • Expanded use of computer generated 3D anatomical reconstructions • Use of in silico technology to select promising drug therapies prior to animal testing • Gene and stem cell therapy
Clinical research	• Use of PDE5I as a prophylactic agent • Efficacy of second generation PDE5I	• Clinical studies of ROCK inhibitors and guanylate cyclase activators • Integration of qualitative studies of ED in clinical practice
Epidemiological research	• ED as a consequence of metabolic and cardiovascular disease • Validity of IIEF in men of different ethnicities	• ED as a *marker* for subclinical metabolic syndrome or cardiovascular disease • Validity of IIEF in MSM and less studied ethnic or racial minorities • Optimization of internet survey based studies

populations. However, concerns remain about the veracity of participant responses. Validity becomes an even more critical issue since the absence of face to face interaction makes the potential for misinterpretation of study questions a very real and salient one [109].

Solicitation of participants from disease focused websites may facilitate research but give a skewed notion of the prevalence of sexual issues. For instance, a recent study reported a very high prevalence of sexual concerns in men prescribed the drug finasteride. While the reported prevalence of problems was very high in the study population, the authors selected patients from a website that is designed for men who report problems from prior use of this drug class [110, 111]. Similarly, an historical study on the perceptions of women on partner circumcision status was drawn in large part from solicitations placed in an anti-circumcision newsletter. Not surprisingly, a very high proportion of female respondents reported lower satisfaction during sexual activity with an uncircumcised male partner [112]. A Danish study reported higher prevalence of sexual problems in circumcised men and female partners of circumcised men [113]. The study enrolled a large and representative population of Danes but it is unclear whether the results could be extrapolated to regions where circumcision is more common (e.g., the USA) (Table 26.2).

Conclusions

Research in erectile dysfunction remains complex and dynamic at all levels. From cell cultures, organ baths, human biopsy specimens, and animal models, we have a strong understanding of the molecular, cellular, and structural factors that make the penis erect. The advent of gene and stem cell technology will now allow us to further use this knowledge for specific drug therapies in diverse patient populations with different underlying etiologies for erectile dysfunction. The development of validated questionnaires such as the International Index of Erectile Function has helped us study the efficacy of current therapies. However, our increasing recognition of the limitations of these study metrics in more diverse patient populations will help us develop more precise studies in the future. Research in erectile dysfunction is rapidly expanding, and it is without question that the future will yield interesting results.

References

1. National Institutes of Health. Consensus development conference statement. Impotence. 7–9 Dec 1992. Int J Impot Res. 1993;5(4):181–284.
2. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexual-

ity and health among older adults in the United States. N Engl J Med. 2007;357(8):762–74.
3. Fang SC, Rosen RC, Vita JA, Ganz P, Kupelian V. Changes in erectile dysfunction over Time in Relation to Framingham Cardiovascular Risk in the Boston Area Community Health (BACH) Survey. J Sex Med. 2015;12(1):100–8.
4. Gareri P, Castagna A, Francomano D, Cerminara G, De Fazio P. Erectile dysfunction in the elderly: an old widespread issue with novel treatment perspectives. Int J Endocrinol. 2014;2014:878670.
5. Evidence-Based Medicine Working G. Evidence-based medicine. a new approach to teaching the practice of medicine. JAMA. 1992;268(17):2420–5.
6. Creswell JW. Research design: qualitative, quantitative, and mixed methods approaches. 4th ed. Thousand Oaks, CA: Sage; 2014. p. 273, xxix.
7. Savin-Baden M, Major CH. Qualitative research: the essential guide to theory and practice. Abingdon: Routledge; 2012.
8. Concato J, Lawler EV, Lew RA, Gaziano JM, Aslan M, Huang GD. Observational methods in comparative effectiveness research. Am J Med. 2010;123(12 Suppl 1):e16–23.
9. Fowkes FG, Fulton PM. Critical appraisal of published research: introductory guidelines. BMJ. 1991;302(6785):1136–40.
10. Fletcher R, Robert Fletcher MDM, Fletcher SW. Clinical epidemiology: the essentials. Alphen aan den Rijn: Wolters Kluwer Health; 2013.
11. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54–60.
12. Concato J. Observational versus experimental studies: what's the evidence for a hierarchy? NeuroRx. 2004;1(3):341–7.
13. Tabachnick BG, Fidell LS. Experimental designs using ANOVA. Belmont, CA: Thomson/Brooks/Cole; 2007.
14. Reis HT, Judd CM. Handbook of research methods in social and personality psychology. Cambridge: Cambridge University Press; 2014.
15. 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(6):822–30.
16. Higgins JPT, Green S, Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. Chichester: Wiley-Blackwell; 2008. p. 649, xxi.
17. Albaugh J, Wayment R, Köhler T. Quantification of erectile dysfunction after prostate cancer treatment. In: McVary KT, editor. Contemporary treatment of erectile dysfunction. Contemporary endocrinology. Totowa, NJ: Humana; 2011. p. 127–50.
18. Yin RK. Case study research: design and methods. Thousand Oaks, CA: Sage; 2013.
19. Cumming G. Understanding the new statistics: effect sizes, confidence intervals, and meta-analysis. Abingdon: Taylor & Francis; 2013.
20. McBurney D, White T. Research methods. Boston, MA: Cengage Learning; 2009.
21. Aberson CL. Applied power analysis for the behavioral sciences. Abingdon: Taylor & Francis; 2011.
22. Williams JK, Andersson KE, Christ G. Animal models of erectile dysfunction (ED): potential utility of non-human primates as a model of atherosclerosis-induced vascular ED. Int J Impot Res. 2012;24(3):91–100.
23. Liu X, Lin CS, Graziottin T, Resplande J, Lue TF. Vascular endothelial growth factor promotes proliferation and migration of cavernous smooth muscle cells. J Urol. 2001;166(1):354–60.
24. Liu X, Lin CS, Spencer EM, Lue TF. Insulin-like growth factor-I promotes proliferation and migration of cavernous smooth muscle cells. Biochem Biophys Res Commun. 2001;280(5):1307–15.
25. Rajasekaran M, Kasyan A, Allilain W, Monga M. Ex vivo expression of angiogenic growth factors and their receptors in human penile cavernosal cells. J Androl. 2003;24(1):85–90.
26. van der Zee R, Murohara T, Luo Z, Zollmann F, Passeri J, Lekutat C, et al. Vascular endothelial growth factor/vascular permeability factor augments nitric oxide release from quiescent rabbit and human vascular endothelium. Circulation. 1997;95(4):1030–7.
27. Wang T, Soker S, Atala A, Siroky MB, Azadzoi KM. Alterations in angiogenic growth factors and neuronal nitric oxide synthase expression in chronic cavernosal ischemia. Int J Impot Res. 2004;16(5):403–11.
28. De Young L, Bella A, Howard J, Brock G. Arteriogenic erectile dysfunction alters protein expression within the cavernosal tissue in an animal model. J Sex Med. 2005;2(2):199–206.
29. Ning H, Qiu X, Baine L, Lin G, Lue TF, Lin CS. Effects of high glucose on human cavernous endothelial cells. Urology. 2012;80(5):1162.e7–11.
30. Ning H, Lin G, Lue TF, Lin CS. A coculture system of cavernous endothelial and smooth muscle cells. Int J Impot Res. 2013;25(2):63–8.
31. Toque HA, da Silva FH, Calixto MC, Lintomen L, Schenka AA, Saad MJ, et al. High-fat diet associated with obesity induces impairment of mouse corpus cavernosum responses. BJU Int. 2011;107(10):1628–34.
32. Oger S, Behr-Roussel D, Gorny D, Lecoz O, Lebret T, Denoux Y, et al. Combination of doxazosin and sildenafil exerts an additive relaxing effect compared with each compound alone on human cavernosal and prostatic tissue. J Sex Med. 2009;6(3):836–47.
33. Costa WS, Carrerete FB, Horta WG, Sampaio FJ. Comparative analysis of the penis corpora cavernosa in controls and patients with erectile dysfunction. BJU Int. 2006;97(3):567–9.
34. Miyake H, Behnsawy HM, Hinata N, Fujisawa M. Objective assessment of residual nerve tissues in radical prostatectomy specimens by immunohistochemical staining of neuronal nitric oxide synthase-positive nerves and its impact on postoperative erectile function. Urology. 2014;84(6):1395–401.

35. Grein U, Schubert GE. Arteriosclerosis of penile arteries: histological findings and their significance in the treatment of erectile dysfunction. Urol Int. 2002;68(4):261–4.
36. Diallo D, Zaitouna M, Alsaid B, Quillard J, Droupy S, Benoit G, et al. What is the origin of the arterial vascularization of the corpora cavernosa? A computer-assisted anatomic dissection study. J Anat. 2013;223(5):489–94.
37. Chung E, De Young L, Brock GB. Investigative models in erectile dysfunction: a state-of-the-art review of current animal models. J Sex Med. 2011;8(12):3291–305.
38. Lue TF, Takamura T, Umraiya M, Schmidt RA, Tanagho EA. Hemodynamics of canine corpora cavernosa during erection. Urology. 1984;24(4):347–52.
39. Lue TF, Takamura T, Schmidt RA, Palubinskas AJ, Tanagho EA. Hemodynamics of erection in the monkey. J Urol. 1983;130(6):1237–41.
40. Carati CJ, Creed KE, Keogh EJ. Autonomic control of penile erection in the dog. J Physiol. 1987;384:525–38.
41. Schuppli CA, Fraser D, McDonald M. Expanding the three Rs to meet new challenges in humane animal experimentation. Altern Lab Anim. 2004; 32(5):525–32.
42. Magee TR, Ferrini M, Garban HJ, Vernet D, Mitani K, Rajfer J, et al. Gene therapy of erectile dysfunction in the rat with penile neuronal nitric oxide synthase. Biol Reprod. 2002;67(3):1033–41.
43. Vignozzi L, Morelli A, Filippi S, Ambrosini S, Mancina R, Luconi M, et al. Testosterone regulates RhoA/Rho-kinase signaling in two distinct animal models of chemical diabetes. J Sex Med. 2007;4(3):620–30. discussion 31-32.
44. Wingard C, Fulton D, Husain S. Altered penile vascular reactivity and erection in the Zucker obese-diabetic rat. J Sex Med. 2007;4(2):348–62. discussion 62-3.
45. Rajasekaran M, Kasyan A, Jain A, Kim SW, Monga M. Altered growth factor expression in the aging penis: the Brown-Norway rat model. J Androl. 2002;23(3):393–9.
46. Bivalacqua TJ, Kendirci M, Champion HC, Hellstrom WJ, Andersson KE, Hedlund P. Dysregulation of cGMP-dependent protein kinase 1 (PKG-1) impairs erectile function in diabetic rats: influence of in vivo gene therapy of PKG1alpha. BJU Int. 2007;99(6):1488–94.
47. Hurt KJ, Sezen SF, Champion HC, Crone JK, Palese MA, Huang PL, et al. Alternatively spliced neuronal nitric oxide synthase mediates penile erection. Proc Natl Acad Sci U S A. 2006;103(9):3440–3.
48. Werner ME, Meredith AL, Aldrich RW, Nelson MT. Hypercontractility and impaired sildenafil relaxations in the BKCa channel deletion model of erectile dysfunction. Am J Physiol Regul Integr Comp Physiol. 2008;295(1):R181–8.
49. Oudot A, Behr-Roussel D, Poirier S, Sandner P, Bernabe J, Alexandre L, et al. Combination of BAY 60-4552 and vardenafil exerts proerectile facilitator effects in rats with cavernous nerve injury: a proof of concept study for the treatment of phosphodiesterase type 5 inhibitor failure. Eur Urol. 2011;60(5):1020–6.
50. Brioni JD, Nakane M, Hsieh GC, Moreland RB, Kolasa T, Sullivan JP. Activators of soluble guanylate cyclase for the treatment of male erectile dysfunction. Int J Impot Res. 2002;14(1):8–14.
51. Paulmann H, Heimann K. Contribution to the problem of central serous retinal detachment (author's transl). Klin Monbl Augenheilkd. 1975;167(2): 324–32.
52. Albersen M, Shindel AW, Mwamukonda KB, Lue TF. The future is today: emerging drugs for the treatment of erectile dysfunction. Expert Opin Emerg Drugs. 2010;15(3):467–80.
53. Lin CS, Xin ZC, Wang Z, Lin G, Lue TF. Molecular Yin and Yang of erectile function and dysfunction. Asian J Androl. 2008;10(3):433–40.
54. Hannan JL, Albersen M, Kutlu O, Gratzke C, Stief CG, Burnett AL, et al. Inhibition of Rho-kinase improves erectile function, increases nitric oxide signaling and decreases penile apoptosis in a rat model of cavernous nerve injury. J Urol. 2013;189(3):1155–61.
55. Sezen SF, Lagoda G, Musicki B, Burnett AL. Hydroxyl fasudil, an inhibitor of Rho signaling, improves erectile function in diabetic rats: a role for neuronal ROCK. J Sex Med. 2014;11(9):2164–71.
56. Donatucci C, Eardley I, Buvat J, Gittelman M, Kell P, Segerson T, et al. Vardenafil improves erectile function in men with erectile dysfunction irrespective of disease severity and disease classification. J Sex Med. 2004;1(3):301–9.
57. Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Raillard P. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J Clin Pract. 2010;64(2):240–55.
58. Mulhall J, Land S, Parker M, Waters WB, Flanigan RC. The use of an erectogenic pharmacotherapy regimen following radical prostatectomy improves recovery of spontaneous erectile function. J Sex Med. 2005;2(4):532–40. discussion 40-2.
59. Ferrini MG, Kovanecz I, Sanchez S, Umeh C, Rajfer J, Gonzalez-Cadavid NF. Fibrosis and loss of smooth muscle in the corpora cavernosa precede corporal veno-occlusive dysfunction (CVOD) induced by experimental cavernosal nerve damage in the rat. J Sex Med. 2009;6(2):415–28.
60. Vignozzi L, Filippi S, Morelli A, Ambrosini S, Luconi M, Vannelli GB, et al. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. J Sex Med. 2006;3(3):419–31.
61. Montorsi F, Brock G, Lee J, Shapiro J, Van Poppel H, Graefen M, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54(4):924–31.

62. Montorsi F, Brock G, Stolzenburg JU, Mulhall J, Moncada I, Patel HR, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol. 2014;65(3):587–96.
63. Zelefsky MJ, Shasha D, Branco RD, Kollmeier M, Baser RE, Pei X, et al. Prophylactic sildenafil citrate improves select aspects of sexual function in men treated with radiotherapy for prostate cancer. J Urol. 2014;192(3):868–74.
64. Pisansky TM, Pugh SL, Greenberg RE, Pervez N, Reed DR, Rosenthal SA, et al. Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: the Radiation Therapy Oncology Group [0831] randomized clinical trial. JAMA. 2014;311(13):1300–7.
65. Kim BH, Lim HS, Chung JY, Kim JR, Lim KS, Sohn DR, et al. Safety, tolerability and pharmacokinetics of udenafil, a novel PDE-5 inhibitor, in healthy young Korean subjects. Br J Clin Pharmacol. 2008;65(6):848–54.
66. Paick JS, Ahn TY, Choi HK, Chung WS, Kim JJ, Kim SC, et al. Efficacy and safety of mirodenafil, a new oral phosphodiesterase type 5 inhibitor, for treatment of erectile dysfunction. J Sex Med. 2008;5(11):2672–80.
67. Maseroli E, Corona G, Rastrelli G, Lotti F, Cipriani S, Forti G, et al. Prevalence of endocrine and metabolic disorders in subjects with erectile dysfunction: a comparative study. J Sex Med. 2015;12(4):956–65.
68. 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(1):54–61.
69. Derosa G, Romano D, Tinelli C, D'Angelo A, Maffioli P. Prevalence and associations of erectile dysfunction in a sample of Italian males with type 2 diabetes. Diabetes Res Clin Pract. 2015;108(2): 329–35.
70. Weinberg AE, Eisenberg M, Patel CJ, Chertow GM, Leppert JT. Diabetes severity, metabolic syndrome, and the risk of erectile dysfunction. J Sex Med. 2013;10(12):3102–9.
71. Yao F, Liu L, Zhang Y, Huang Y, Liu D, Lin H, et al. Erectile dysfunction may be the first clinical sign of insulin resistance and endothelial dysfunction in young men. Clin Res Cardiol. 2013;102(9):645–51.
72. Guo W, Liao C, Zou Y, Li F, Li T, Zhou Q, et al. Erectile dysfunction and risk of clinical cardiovascular events: a meta-analysis of seven cohort studies. J Sex Med. 2010;7(8):2805–16.
73. Pastuszak AW, Hyman DA, Yadav N, Godoy G, Lipshultz LI, Araujo AB, et al. Erectile dysfunction as a marker for cardiovascular disease diagnosis and intervention: a cost analysis. J Sex Med. 2015;12(4):975–84.
74. Hirshfield S, Chiasson MA, Wagmiller Jr RL, Remien RH, Humberstone M, Scheinmann R, et al. Sexual dysfunction in an Internet sample of U.S. men who have sex with men. J Sex Med. 2010; 7(9):3104–14.
75. Shindel AW, Vittinghoff E, Breyer BN. Erectile dysfunction and premature ejaculation in men who have sex with men. J Sex Med. 2012;9(2):576–84.
76. Vansintejan J, Vandevoorde J, Devroey D. The GAy MEn Sex StudieS: erectile dysfunction among Belgian gay men. Int J Gen Med. 2013;6:527–34.
77. Carvalheira AA, Pereira NM, Maroco J, Forjaz V. Dropout in the treatment of erectile dysfunction with PDE5: a study on predictors and a qualitative analysis of reasons for discontinuation. J Sex Med. 2012;9(9):2361–9.
78. McCabe MP, O'Connor EJ, Conaglen JV, Conaglen HM. The impact of oral ED medication on female partners' relationship satisfaction. J Sex Med. 2011; 8(2):479–83.
79. Hartman ME, Irvine J, Currie KL, Ritvo P, Trachtenberg L, Louis A, et al. Exploring gay couples' experience with sexual dysfunction after radical prostatectomy: a qualitative study. J Sex Marital Ther. 2014;40(3):233–53.
80. Pandey AS. Basic science research in medicine. Kathmandu Univ Med J. 2010;8(31):292–3.
81. Traish AM, Goldstein I, Kim NN. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. Eur Urol. 2007;52(1):54–70.
82. Andersson KE. Mechanisms of penile erection and basis for pharmacological treatment of erectile dysfunction. Pharmacol Rev. 2011;63(4):811–59.
83. Li Y, Wu W, Ren H, Wang J, Zhang S, Li G, et al. Exploring the structure determinants of pyrazinone derivatives as PDE5 3HC8 inhibitors: an in silico analysis. J Mol Graph Model. 2012;38:112–22.
84. Ekins S, Mestres J, Testa B. In silico pharmacology for drug discovery: applications to targets and beyond. Br J Pharmacol. 2007;152(1):21–37.
85. Valerio Jr LG. In silico toxicology for the pharmaceutical sciences. Toxicol Appl Pharmacol. 2009; 241(3):356–70.
86. Hatzimouratidis K, Burnett AL, Hatzichristou D, McCullough AR, Montorsi F, Mulhall JP. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. Eur Urol. 2009;55(2):334–47.
87. Burnett AL. Rationale for cavernous nerve restorative therapy to preserve erectile function after radical prostatectomy. Urology. 2003;61(3):491–7.
88. Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? Drugs. 2005;65(12):1621–50.
89. Washington SL, Shindel III AW. A once-daily dose of tadalafil for erectile dysfunction: compliance and efficacy. Drug Des Devel Ther. 2010;4:159–71.
90. Ouyang B, Sun X, Han D, Chen S, Yao B, Gao Y, et al. Human urine-derived stem cells alone or

genetically-modified with FGF2 Improve type 2 diabetic erectile dysfunction in a rat model. PLoS One. 2014;9(3), e92825.
91. Strong TD, Gebska MA, Burnett AL, Champion HC, Bivalacqua TJ. Endothelium-specific gene and stem cell-based therapy for erectile dysfunction. Asian J Androl. 2008;10(1):14–22.
92. Lemon R, Dunnett SB. Surveying the literature from animal experiments. BMJ. 2005;330(7498):977–8.
93. Shanks N, Greek R, Greek J. Are animal models predictive for humans? Philos Ethics Humanit Med. 2009;4:2.
94. Hackam DG. Translating animal research into clinical benefit. BMJ. 2007;334(7586):163–4.
95. Mason S, Hussain-Gambles M, Leese B, Atkin K, Brown J. Representation of South Asian people in randomised clinical trials: analysis of trials' data. BMJ. 2003;326(7401):1244–5.
96. Sheikh A, Netuveli G, Kai J, Panesar SS. Comparison of reporting of ethnicity in US and European randomised controlled trials. BMJ. 2004;329(7457): 87–8.
97. Wendler D, Kington R, Madans J, Van Wye G, Christ-Schmidt H, Pratt LA, et al. Are racial and ethnic minorities less willing to participate in health research? PLoS Med. 2006;3(2), e19.
98. Langford AT, Resnicow K, Dimond EP, Denicoff AM, Germain DS, McCaskill-Stevens W, et al. Racial/ethnic differences in clinical trial enrollment, refusal rates, ineligibility, and reasons for decline among patients at sites in the National Cancer Institute's Community Cancer Centers Program. Cancer. 2014;120(6):877–84.
99. Derby CA, Araujo AB, Johannes CB, Feldman HA, McKinlay JB. Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging Study. Int J Impot Res. 2000;12(4):197–204.
100. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research. Alphen aan den Rijn: Wolters Kluwer Health; 2013.
101. Chow SC, Wang H, Shao J. Sample size calculations in clinical research. 2nd ed. Abingdon: Taylor & Francis; 2007.
102. Hirsch M, Donatucci C, Glina S, Montague D, Montorsi F, Wyllie M. Standards for clinical trials in male sexual dysfunction: erectile dysfunction and rapid ejaculation. J Sex Med. 2004;1(1):87–91.
103. Walsh PC, Marschke P, Ricker D, Burnett AL. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology. 2000;55(1):58–61.
104. Mulhall JP, King R, Kirby M, Hvidsten K, Symonds T, Bushmakin AG, et al. Evaluating the sexual experience in men: validation of the sexual experience questionnaire. J Sex Med. 2008;5(2):365–76.
105. Rosen RC, Catania J, Pollack L, Althof S, O'Leary M, Seftel AD. Male Sexual Health Questionnaire (MSHQ): scale development and psychometric validation. Urology. 2004;64(4):777–82.
106. Sperling H, Debruyne F, Boermans A, Beneke M, Ulbrich E, Ewald S. The POTENT I randomized trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. J Sex Med. 2010;7(4 Pt 1): 1497–507.
107. Aghighi A, Grigoryan VH, Delavar A. Psychological determinants of erectile dysfunction among middle-aged men. Int J Impot Res. 2015;27(2):63–8.
108. Steckler A, McLeroy KR. The importance of external validity. Am J Public Health. 2008; 98(1):9–10.
109. van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? Am J Epidemiol. 2010;172(11):1292–8.
110. Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. J Sex Med. 2011;8(6):1747–53.
111. Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? J Sex Med. 2012;9(11):2927–32.
112. O'Hara K, O'Hara J. The effect of male circumcision on the sexual enjoyment of the female partner. BJU Int. 1999;83 Suppl 1:79–84.
113. Frisch M, Lindholm M, Gronbaek M. Male circumcision and sexual function in men and women: a survey-based, cross-sectional study in Denmark. Int J Epidemiol. 2011;40(5):1367–81.

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