University of Naples "Federico II"

PhD Program in Neuroscience
XXXV Cycle

Course Director: *Prof. Maurizio Taglialatela*

PhD Thesis

Erectile dysfunction and obstructive sleep apnoea: a cross-sectional clinical study

Tutor:
Prof. Ciro Imbimbo

Candidate:
Dott. Felice Crocetto

Academic Year 2021-2022

Il talento prende forma
quando incontra la Guida
che gli fornisce l'opportunità

Index

Abstract

State of the art: Erectile Dysfunction (ED) is the inability to achieve or maintain an erection for satisfactory sexual performance. Recently, it has been suggested that obstructive sleep apnoea (OSA) can induce ED. Sleep fragmentation and sympathetic hyperactivity after OSA that induce reduced nocturnal erections in the rapid eye movement (REM) periods and hormonal status modifications, as well as comorbidities observed in both diseases could be involved in the ED pathogenesis.

Purpose: In this study the impact of nonendocrine (neurogenic, vasculogenic and iatrogenic) and endocrine pathways involved in ED pathogenesis have been analyzed. In particular, a cross-sectional study has been performed to investigate the prevalence and clinical characteristics of ED in patients with OSA.

Methods: We enrolled 133 male patients with suspected OSA. Ear, nose and throat evaluation, laboratory tests, body mass index, Epworth sleepiness scale, 5-international index of erectile function, overnight ambulatory polygraphy and drug-induced sleep endoscopy patterns were assessed. Eighty patients reported OSA. 60% (n = 48) reported ED.

Results: Statistically significant correlations were found between 5-International Index of Erectile Function and age, hypertension, diabetes, Epworth sleepiness scale, apnoea-hypopnea index score, O_2 saturation-nadir, and oxygen desaturation index. Age, diabetes and O_2 saturation-nadir were independent predictors of ED. Epworth sleepiness scale, apnoea-hypopnea index score, O_2 saturation-nadir, oxygen desaturation index and albumin were higher compared to patients without ED. No statistically significant differences were reported for drug-induced sleep endoscopy patterns and ED.

Conclusions: This study confirmed that OSA is a risk factor for ED. In particular, our data demonstrated that OSA parameters correlate with ED and age, while $SatO_2$-nadir and diabetes are independent predictors of ED. Our research pointed out that men presenting to the Ear, nose and throat (ENT) clinic with OSA are at significant risk of having ED. Therefore, males with OSA should be investigated for ED.

Keywords: Erectile Dysfunction (ED), Obstructive sleep apnoea (OSA), ED etiopathogenesis; Aging; Diabetes mellitus; Hypertension; SatO2; Sex-hormones; ED management; ED treatment.

1. Introduction

Erectile Dysfunction (ED) represents the inability to achieve or maintain an erection for satisfactory sexual performance. ED affects a relevant number of men at least occasionally (Yafi et al., 2016). ED shows a high prevalence and incidence worldwide (Eardley, 2013). ED prevalence is higher in the United States, as well as in Eastern and South-eastern Asian countries, rather than in Europe or South America. Nevertheless, these differences could be related to cultural or socioeconomic factors. Two milestone studies, the Massachusetts Male Aging Study (MMAS) and the European Male Ageing Study (EMAS) (Corona et al., 2010; Feldman et al., 1994) are among the largest studies which have analysed ED prevalence. The MMAS reported a mild to moderate ED prevalence in 52% of men aged 40–70 years in the Boston area; with a specific prevalence for minimal, moderate, and complete ED of 17.2%, 25.2%, and 9.6%, respectively. (Feldman et al., 1994) The EMAS, instead, the largest European multicentre population-based study of ageing men (40–79 years), showed an ED average prevalence of 30% ranging, from 6% to 64% depending on different age subgroups, which increased with age (Corona et al., 2010) (Fig. 1).

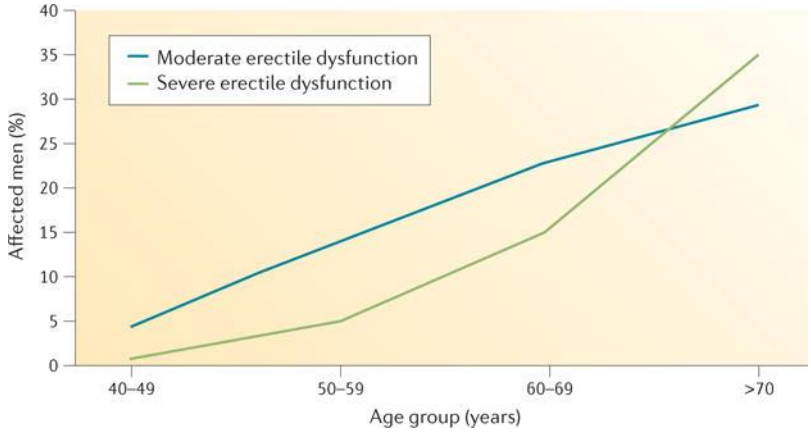

Figure 1: Increasing prevalence of ED with age (Yafi et al., 2016)

In addition, the Cologne study, revealed an ED prevalence in men aged 30-80 years of 19.2%, with a steep age-related increase from 2.3% to 53.4% (Braun et al., 2000). Similarly, the incidence rate of ED was 19.2% (mean follow-up of 4.2 years) in a Dutch study (Schouten et al., 2005). In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED (Capogrosso et al., 2013). Further studies are needed to assess the influence of genetic background and the possible interaction with environmental conditions.

ED often impacts negatively on interpersonal relationships, mood and quality of life. Alterations of the reflex erection (achieved by directly touching the penile shaft, which is under the control of the peripheral nerves and the lower parts of the spinal cord) and psychogenic erection (achieved by erotic or emotional stimuli, using the limbic system of the brain), the two major aspects of male erection responsible of ED, are the target of therapeutic intervention. According to the five-item International Index of Erectile Function (IIEF-5) questionnaire, the ED severity is described as mild (score 8–11), moderate (score 8–11) or severe (score 1–7) while a 22–25 score indicates no ED. Although ED was considered a psychogenic disorder in the past, current evidence suggests an organic aetiology for more than 80% of cases (Fig. 2).

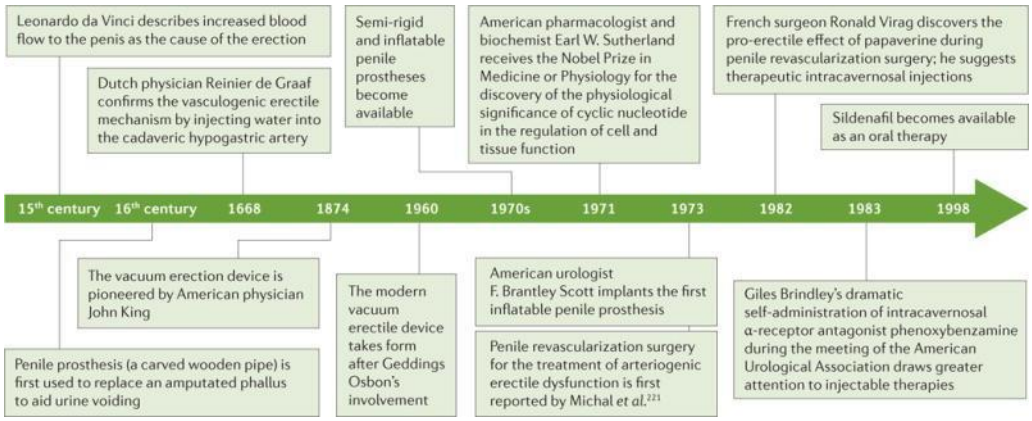

Figure 2: Timeline of the understanding and treatment of ED (Yafi et al., 2016)

Organic ED causes are grouped into nonendocrine and endocrine. While reduced serum testosterone levels represent the main endocrine factor responsible for ED, among nonendocrine causes, vasculogenic ones represent the most common and involve arterial inflow and venous outflow alterations albeit neurogenic and iatrogenic aetiologies have also been described (Yafi et al., 2016). In addition, it has been recently shown that obstructive sleep apnoea (OSA) could also induce ED (Hoyos et al., 2015). Although the exact mechanism linking OSA and ED is not well established, it has been proposed the role of comorbidities observed in both diseases, such as diabetes, hypertension and metabolic syndrome in inflammation and vascular impairment (Bouloukaki et al., 2014; Hoyos et al., 2015; Kellesarian et al., 2018). Additionally, sleep fragmentation and sympathetic hyperactivity after OSA, which reduce nocturnal erections in the rapid eye movement (REM) periods, and hormonal status modifications could be involved in the ED pathogenesis (Andersen et al., 2010).

2. Etiopathogenesis of Erectile Dysfunction

The smooth muscle contraction is responsible for the flaccid state of the penis. A combination of adrenergic (noradrenaline), myogenic and endothelium-derived (prostaglandin and endothelin) contracting factors regulate smooth muscle contraction (Fig. 3) (Andersson & Wagner, 1995; Lue, 2000; Saenz de Tejada et al., 1989).

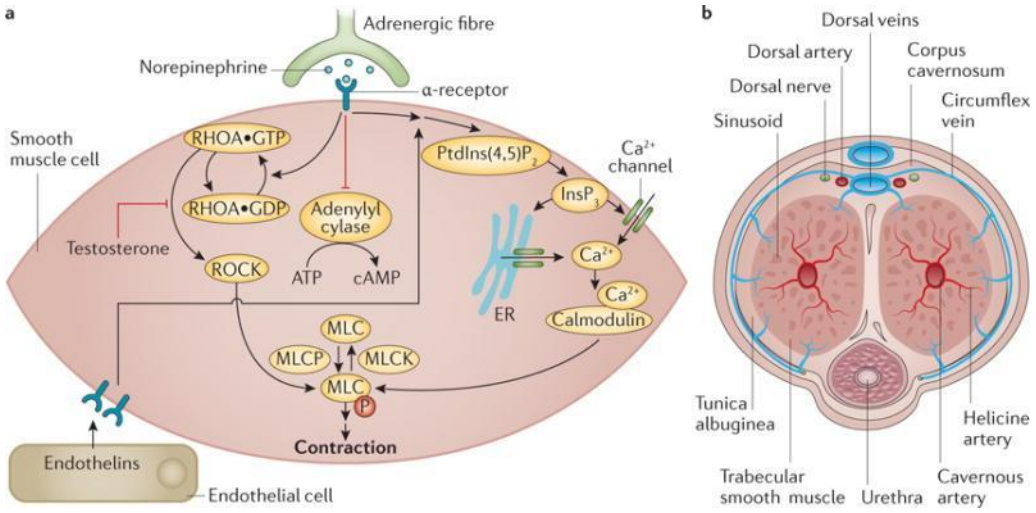

Figure 3: Penile smooth muscle contraction — the flaccid state

a | Ca^{2+} influx into cells is regulated by noradrenaline signalling and inositol-1,4,5-trisphosphate (Ins (1,4,5) P3 levels, produced from phosphatidylinositol-4,5-bisphosphate (PtdIns (4,5) P2) by phospholipase C); increased intracellular Ca^{2+} binds to calmodulin, facilitating the calmodulin–myosin light chain kinase (MLCK) complex formation. This leads to MLC phosphorylation, resulting in smooth muscle contraction and a flaccid penis. Noradrenaline signalling also inhibits adenylyl cyclase and modulates the RHO-associated protein kinase (ROCK) pathway, which increases the sensitivity of MLC to Ca^{2+}, a process negatively regulated by testosterone. Endothelins and prostaglandins from the endothelium also trigger an increase in intracellular Ca^{2+} to promote smooth muscle contraction.
b | When the smooth muscle is contracted, the inflow of blood through the cavernous artery is minimal, and the blood outflows freely through the subtunical venular plexus. ER, endoplasmic reticulum; MLCP, myosin light chain phosphatase (Yafi et al., 2016).

The Nitric oxide (NO) release from non-adrenergic noncholinergic (NANC) nerve fibres and acetylcholine release from parasympathetic cholinergic nerve fibres induce erection upon sexual stimulation (Fig. 4). Subsequently, the signalling pathways activation increases cyclic GMP (cGMP) concentrations, decreases intracellular Ca^{2+} levels and smooth muscle cell relaxation (Lue, 2000; Lue & Tanagho, 1987). Upon smooth muscle relaxation, blood fills the lacunar spaces in the corpora cavernosa, subtunical venules are compressed, and the venous outflow (veno-occlusion) is blocked. Phosphodiesterase type 5 (PDE5) reverted the process by cGMP hydrolysis (Lue, 2000; Lue & Tanagho, 1987). ED could occur when any of these processes are interrupted.

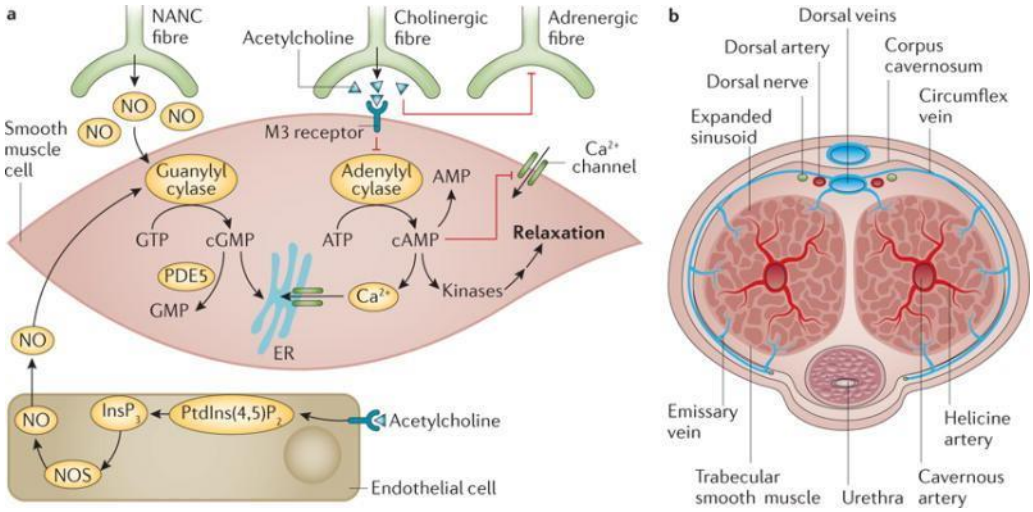

Figure 4: Penile smooth muscle relaxation — the erect state

a | Upon sexual stimulation, normal erection occurs after nitric oxide (NO) release from non-adrenergic non-cholinergic (NANC) nerve fibres causes the activation of guanylyl cyclase, which raises the concentration of cyclic GMP, and after parasympathetic cholinergic nerve fibres release acetylcholine, which activates adenylyl cyclase to increase the levels of cyclic AMP. Signalling pathways that are triggered decrease intracellular Ca^{2+} levels and lead to smooth muscle cell relaxation.
b | As the smooth muscle relaxes, blood is able to fill the lacunar spaces in the cavernosa, leading to compression of the subtunical venules, thereby blocking the venous outflow.

The process is reversed as cGMP is hydrolysed by phosphodiesterase type 5 (PDE5). ER, endoplasmic reticulum; InsP3, inositol trisphosphate; NOS, NO synthase; PtdIns (4,5) P2, phosphatidylinositol 4,5 bisphosphate (Yafi et al., 2016).

2.1 Nonendocrine causes

Psychogenic factors related to ED

Stress, depression and anxiety are generally related to the inability to achieve and maintain an erection before or during sexual relations and are commonly associated with psychogenic ED. Thus, non-organic ED causes, such as psychogenic or adrenaline-mediated ED (noradrenaline-mediated or sympathetic-mediated ED) are relevant factors that should be considered in ED evaluation and management. This association is unsurprising, given that noradrenaline is the primary erectolytic (anti-erectile) neurotransmitter (McCabe & Althof, 2014).

Neurogenic

Neurogenic ED, caused by a nerve signalling deficit to corpora cavernosa, could be seconddary to several diseases such as spinal cord injury, multiple sclerosis, Parkinson's disease, lumbar disc disease, traumatic brain injury, radical pelvic surgery (radical prostatectomy, radical cystectomy, abdominoperineal resection) and diabetes. Upper motor neuron lesions (above spinal nerve T10) do not result in local changes in the penis but could inhibit the central nervous system (CNS)-mediated control of the erection. By contrast, sacral lesions (S2–S4 are typically responsible for reflexogenic erections) causing functionnal and structural alterations owing to the decreased innervation (Brackett et al., 2010). Such injuries reduce the smooth muscle NO availability. The apoptosis of smooth muscle and endothelial cells of the blood vessels, as well as upregulation of fibrogenetic cytokines leading to smooth muscle collagen deposition, promotes the changes that result

in veno-occlusive dysfunction (venous leak) (Monica G Ferrini, Kovanecz, et al., 2006; Monica G Ferrini, Davila, et al., 2006; Monica G Ferrini et al., 2009; Leungwattanakij et al., 2003; John P Mulhall et al., 2008).

Vasculogenic

Vascular disease and endothelial dysfunction lead to ED through reduced blood inflow, arterial insufficiency or arterial stenosis. Vasculogenic ED is the most common cause of organic ED. The risk of developing vasculogenic ED is increased in men with hypertension (odds ratio (OR) of 3.04 for those on anti-hypertensive medication, and 1.35 for those not on medication), diabetes (OR 2.57) and dyslipidaemia (OR 1.83) (Bacon et al., 2006; Francis et al., 2007; Kupelian et al., 2010; Wei et al., 1994). Cigarette smoking has also been shown to increase the risk of ED (OR 1.4) (Bacon et al., 2006; Francis et al., 2007; McVary et al., 2001; (Brackett et al., 2010). Vasculogenic ED is secondary to the arterial wall changes (decreased elasticity) in response to the blood pressure increase. In addition, atherosclerosis related to diabetes, dyslipidaemia and/or cigarette smoking can lead to arterial stenosis and induce vascular injury. Hypoxia of corpora cavernosal can cause a decrease in prostaglandin E1 levels, which inhibit pro-fibrotic cytokines, such as transforming growth factor β1 (TGFβ1) (Moreland et al., 1995). These pro-fibrotic cytokines promote collagen deposition, replacing the smooth muscle and resulting in decreased penis elasticity (Moreland, 1998). Consequently, the ability of the cavernosa to compress the subtunical veins decreases, leading to corporal veno-occlusive dysfunction (A Nehra et al., 1996).

Iatrogenic

Radical pelvic surgery represents the most common iatrogenic cause of ED. Generally, these procedures could primarily induce neurogenic damage (cavernous nerve injury) and, in some cases, pudendal artery injury (Tal, Valenzuela, et al., 2009). Similarly, pelvic fractures could cause ED in an analogous manner, owing to nerve distraction injury and arterial trauma. Various medications have also been shown to be associated with ED development: thiazide diuretics and β-blockers, used in the treatment of hypertension are well-known associated with ED, but others, such as psychotherapeutics, anti-androgens, anti-ulcer drugs, opiates and digoxin, could also induce ED (Francis et al., 2007). However, whether the ED results directly from the medication itself or the underlying disease - for example, hypertension - is difficult to define. The Treatment of Mild Hypertension Study (TOMHS) compared five anti-hypertensive drugs with a placebo for quality-of-life modifycations (Grimm et al., 1997). Chlorthalidone (a diuretic drug used to treat hypertension) had the greatest effect on sexual function at 2 years after treatment, but the placebo achieved a similar result at 4 years. Accordingly, chlorthalidone may potentiate ED earlier in those who are likely to develop the condition later in life.

2.2 Endocrine causes

Androgens are considered the major hormonal regulator of penile development and physiology (Baskin et al., 1997; Boas et al., 2006). However, the role of testosterone replacement therapy in ED is controversial due to the discrepancies in the findings from clinical trials. In addition, hypogonadism and ED are common in ageing. The increasing association of ED and the progressive decline of androgen levels with ageing does not necessarily imply a causal link. Studies performed to understand the role of reduced testosterone on erectile function focused on androgen ablation - a model that cannot be easily translated to ED in humans- permitted to describe three sites of action for androgens: the nuclei in the CNS52, the spinal neurons and pelvic ganglia, and the genital tissues (Filippi et al., 2009; Vignozzi et al., 2007) (Isidori et al., 2014) (Fig. 5).

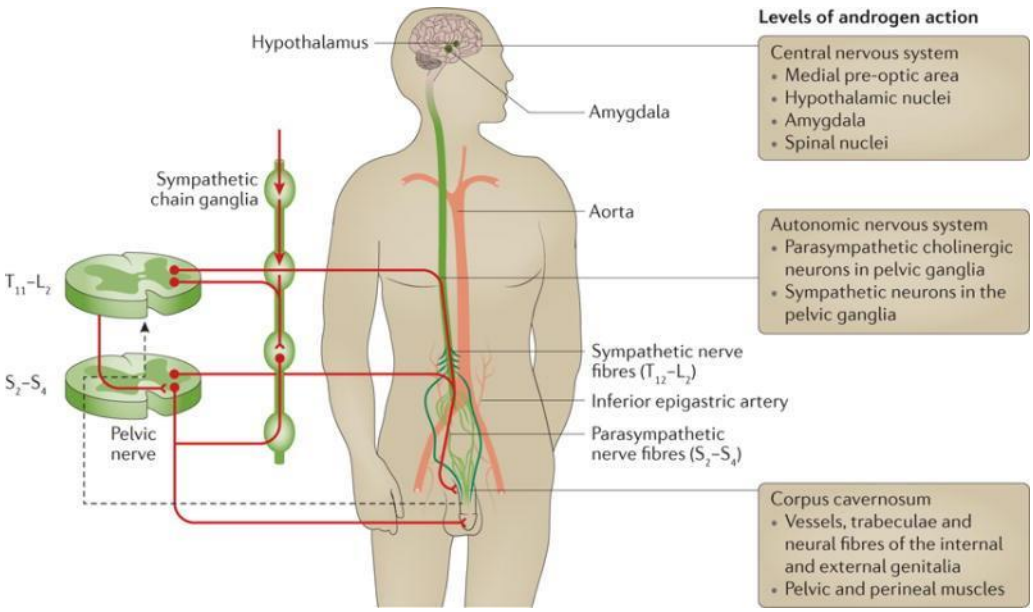

Figure 5: Levels of androgen action in the control of sexual response (Yafi et al., 2016)

Albeit part of the erectile response to testosterone is mediated through sexual desire, it has been also reported a direct role of testosterone on cavernous smooth muscle cells, involving NO, RHO-associated protein kinase (ROCK), PDE5 and the adrenergic response.

Effects on smooth muscle cells

All animal studies support the idea that castration (i.e. the reduction of testosterone levels) causes a rapid drop in intracavernous pressure, owing to both reduced arterial inflow and altered veno-occlusion during stimulated erections (Mills et al., 1998). Castration is indeed associated with a rapid reduction in neuronal nitric oxide synthase (nNOS) (Lugg et al., 1996) and pelvic ganglion activity (Giuliano et al., 1993). However, in hypogonadism and castration models, the effects of testosterone replacement on nNOS have been variable, with some studies revealing increased expression but unaltered activity while other showing no effect (Lugg et al., 1996; A M Traish et al., 1999). Studies carried out in animals treated with l-NG-nitroargininemethyl ester (l-NAME, a NOS inhibitor) revealed that androgens trigger an additional NO-independent mechanisms that still require intact cGMP generation to control veno-occlusion. (Reilly, Lewis, et al., 1997) As result, androgens require cGMP to produce an erection, which suggests that androgens modulate the erectile response through redundant mechanisms involving cGMP generation. Among these NO-independent targets, the ROCK pathway, (Sopko et al., 2014) contributes to tonic smooth muscle cell contraction via calcium sensitization. Hypogonadism has been shown to induce activation of ROCK1, which counteracts smooth muscle cell relaxation. However, hypogonadism does not activate ROCK2, which is increased in response to testosterone in endothelial cells (Liao et al., 2013). Additional studies are necessary to understand the role of androgens in ROCK-dependent modulation of erection. NO-independent, pro-erectile mechanisms of androgens also include regulation of expression of smooth muscle myosin

isoforms (X.-H. Zhang et al., 2011) and sphingosine-1-phosphate (S1P) (di Villa Bianca et al., 2006; Ohmori et al., 2003) binding to its natural receptors: a family of G protein-coupled receptors that are widely expressed in the cardiovascular system. S1P receptor activation sustains constriction of smooth muscle cells via phospholipase C (which cleaves phosphatidylinositol-4,5-bisphosphate (PtdIns (4,5) P2) into inositol-1,4,5-trisphosphate (Ins (1,4,5) P3), leading to increased Ca^{2+}) and the ROCK pathways. In endothelial cells, F1P receptor activation triggers the phosphoinositide 3-kinase (PI3K)–AKT pathway, enabling crosstalk between the ROCK and the endothelial nitric oxide synthase (eNOS) pathways. (X.-H. Zhang et al., 2011) The latter findings reinforce the beneficial role of androgens on several overlapping NO-independent pathways (F1P, PI3K–AKT and ROCK) favouring erectile response. Several studies in vitro, using animal and human tissues, have shown that PDE5 expression is upregulated by androgens (Morelli et al., 2004; A M Traish et al., 1999; X.-H. Zhang et al., 2005). However, recent studies have questioned this evidence, suggesting that low PDE5 in hypogonadism simply reflects the overall reduction in smooth muscle cell content (Yang et al., 2009). Indeed, androgen deprivation triggers apoptosis of smooth muscle cells, extracellular matrix deposition (A M Traish et al., 1999) and accumulation of lipid droplets in mesenchymal cells (especially in the subtunical region) contributing to impaired veno-occlusion (Abdulmaged M Traish et al., 2005). In general, cGMP levels, regulated by the activity of PDE5 (the primary enzyme involved in cGMP degradation), seem crucial for any direct (Morelli et al., 2004; A M Traish et al., 1999; X.-H. Zhang et al., 2005) or indirect (Andric et al., 2010) androgenic regulation within the penis (Mills et al., 1998). A recognized mechanism of action of testosterone is the regulation of α1-adrenergic responsiveness of smooth muscle cells (Reilly, Stopper, et al., 1997; A M Traish et al., 1999). Castration in animals has also been shown to be associated with a decreased density of NANC innervating fibres and reduced NANC-mediated rela-

xation in isolated corpora cavernosa strips (A M Traish et al., 1999). These data suggest an effect of testosterone on the postganglionic parasympathetic neurons, or even further upstream within the autonomic nervous system (Andrea M Isidori et al., 2014). In line with this hypothesis, the effects of castration on penile haemodynamics, including NOS activity, can be transiently reversed in vivo by short-term electrical stimulation of the cavernosal nerve (Lugg et al., 1996). Accordingly, androgens might be necessary to support adequate neuronal stimulation to the corpora cavernosa, maintaining tissue structural integrity; denervation, as can occur following prostate surgery, and castration share some histological similarities (Andrea M Isidori et al., 2014).

Hypogonadism

In the 1980s, Bancroft performed pivotal studies to discriminate central effects from peripheral effects of testosterone replacement therapy. In acute settings, erectile capacity in response to visual stimulation is less sensitive to androgen than sexual interest, fantasies and cognitive sexual activities (Bancroft & Wu, 1983). Androgen enhances the sexual response to sexual fantasy more than it enhances the response to visual stimuli, which has implications for the kind of sexual activity measured in the research setting. Experimental endogenous hypogonadism induced by gonadotropin-releasing hormone (GnRH) agonists (Gray et al., 2005) (Buena et al., 1993) revealed that at least 8 nM of testosterone is required for erectile function. However, some hypogonadal men retain near-normal sexual activity despite very low testosterone levels (Kwan et al., 1983). In young adults, the androgen dependency of erectile function is maintained at threshold values that are far below those required to maintain the function of other target organs (that is, <8 nM or 230 ng/dl). However, erectile function, despite low androgen levels, may not apply to elderly men who have comorbidities, possibly owing to changes in androgen receptor expression and acti-

vity. To match testosterone levels to an individual's own requirement, the concept of compensated or subclinical hypogonadism (Giannetta et al., 2012) has been introduced. In this setting, it is suggested that when testosterone declines from a previously higher level, a rise in the levels of luteinizing hormone might be a biomarker for insufficient androgenization (Giannetta et al., 2012; Tajar et al., 2010). Other evidence for the role of testosterone in ED derives from clinical trials on testosterone replacement therapy. The few available randomized clinical trials (RCT) addressing the roles of testosterone treatment in ED have been extensively reviewed, with the largest and most updated meta-analysis confirming significant beneficial effects on various domains of erectile function, but only in men with testosterone levels of less than 12 nM (345 ng/dl) at baseline (Corona et al., 2014). Regression and subgroup analyses emphasized the role of ageing as a possible moderator of responsiveness to testosterone in those with ED (Corona et al., 2014). Another relevant emerging aspect is the time course of testosterone effects (i.e., the length of treatment necessary to achieve the maximum result). A systematic review (Saad et al., 2011) and different RCTs (Giltay et al., 2010; Hackett et al., 2013; Isidori et al., 2015) revealed that although the effects on libido, ejaculation and sexual activity were apparent within just 2–3 weeks of commencing treatment, the effects on erectile function may take up to 6–12 months to be evident. Recently, the largest and longest trial addressing the effects of testosterone replacement therapy on subclinical atherosclerosis progression in older men showed no significant difference in IIEF score compared with the placebo at 18 months or 36 months after the start of treatment. However, ED was not an inclusion criterion for the trial, and the relatively high baseline total IIEF score suggests that only some of the participants had ED at enrolment (Basaria et al., 2015). Several studies have recently reported growing concerns regarding the safety of sex steroid replacement therapy. These studies questioned the physiological roles of the various hormones and purposefully sought to

amplify some sort of 'hormonophobia' by exaggerating or misrepresenting safety concerns. (Morgentaler, 2014) However, leaving aside the controversies surrounding both the alarming (Finkle et al., 2014) and reassuring studies (Sharma et al., 2015) - contrasts that impose a risk-benefit evaluation before any treatment - it seems clear that these considerations neither apply to young adults with hypogonadism (Isidori et al., 2015) nor question the physiological role of testosterone in erectile function. Finally, little data have addressed the roles of other hormones in ED (Sansone et al., 2014). Indeed, possible roles have been documented for thyroid hormones, prolactin, growth hormone and insulin-like growth factor 1, dehydroepiandrosterone and oxytocin. Although these hormones play a role in the erection pathophysiology, their epidemiological impact is likely to be small and is awaiting confirmation. After testosterone, prolactin is the most altered hormone in men with sexual dysfunction; its main effect is to inhibit gonadotropin secretion to induce hypogonadism. Thus, prolactin should be considered for screening, together with testosterone and luteinizing hormone in men with ED.

Pelvic surgery and prostate cancer treatment

Pelvic surgery, especially for oncological disease- e.g., radical prostatectomy (RP) (Emanu et al., 2016), radical cystectomy (Modh et al., 2014) and colorectal surgery (Celentano et al., 2017)- may have a negative impact on erectile function and sexual health. The most relevant causal factor is a lesion occurring in the neurovascular bundles that control the complex mechanism of the cavernous erectile response, whose preservation (either partial or complete) during surgery eventually configures nerve-sparing (NS) approach (Walz et al., 2016). Therefore, surgery resulting in damage to the neurovascular bundles is responsible for ED, although NS approaches have been adopted over the last few decades. This approach is applicable to all types of surgery that are potentially harmful to erectile

function, although, to date, only the surgical treatment of prostate cancer (PCa) shows enough scientific evidence supporting its potential pathophysiological association with ED (Capogrosso et al., 2020; Salonia et al., 2017). However, even non-surgical treatments of PCa (i.e., radiotherapy, or brachytherapy) can be associated with ED (Hunt et al., 2021; Nolsøe et al., 2021). The active surveillance for the treatment of PCa has been developed to avoid over-treatment of non-significant localised low-risk diseases, while limiting potential functional adverse effects, including ED. However, it has been suggested that also active surveillance has a detrimental impact on erectile function and sexual well-being (Fenton et al., 2018; Lardas et al., 2017; Martina Maggi et al., 2019). To date, some of the most robust data on PROMs (Phatients Reported Outcome Measures) including erectile function, comparing treatments for clinically localised PCa come from the Prostate Testing for Cancer and Treatment (ProtecT) trial, in which 1,643 patients were randomised to active treatment (either RP or RT) and active monitoring and were followed-up for 6 years (Donovan et al., 2016). Sexual function (including erectile function) and its effect on QoL (Quality of Life) were assessed with the Expanded Prostate Cancer Index Composite with 26 items (EPIC-26) instrument (Szymanski et al., 2010; Volz-Sidiropoulou et al., 2008). At baseline, 67% of men reported erections firm enough for sexual intercourse but this fell to 52% in the active monitoring group, 22% in the RT group, and 12% in the RP group, at 6-months assessment. The worst trend over time was recorded in the RP group (with 21% of erections firm enough for intercourse after 3 years vs. 17% after 6 years). In the RT group, the percentage of men reporting erections firm enough for intercourse increased between 6 and 12 months, with a subsequent decrease to 27% at 6-year assessment. The percentage declined over time on a yearly basis in the active monitoring group, with 41% of men reporting erections firm enough for intercourse at 3 years and 30% at 6-year evaluations (Donovan et al., 2016). Radical prostatectomy (open, laparoscopic or robot-assisted) is a

widely performed procedure with a curative intent for patients presenting with clinically localised intermediate- or high-risk PCa and a life expectancy of > 10 years based on health status and co-morbidity (Mottet et al., 2017). This procedure may lead to treatment-specific sequelae affecting health-related QoL. Men undergoing RP (any technique) should be adequately informed before the operation that there is a significant risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie's-like disease, and changes in penile length. (Nolsøe et al., 2021; Salonia et al., 2017) These outcomes have become increasingly important with the more frequent diagnosis of PCa in both younger and older men. (H. J. Boyle et al., 2019; Salonia et al., 2012) Research has shown that 25-75% of men experience post-RP ED, (Sanda et al., 2008) even though these findings had methodological flaws; in particular, the heterogeneity of reporting and assessment of ED among the studies. (Capogrosso et al., 2020; Tal, Alphs, et al., 2009). Conversely, the rate of unassisted post-operative erectile function recovery ranged between 20 and 25% in most studies. These rates have not substantially improved or changed over the past 17 years, despite growing attention to post-surgical rehabilitation protocols and refinement of surgical techniques. (Capogrosso, Vertosick, et al., 2019; Schauer et al., 2015; Tal, Alphs, et al., 2009) Overall, patient age, baseline erectile function and surgical volume, with the consequent ability to preserve the neurovascular bundles, seem to be the main factors in promoting the highest rates of postoperative potency. (Khoder et al., 2015; Salonia et al., 2012, 2017; Sanda et al., 2008) Regardless of the surgical technique, surgeons' experience may clearly impact on post-operative erectile function outcome; in particular, when surgeons have a caseload greater than 25 radical prostatectomy cases per year or total cumulative experience of >1,000 prostatectomy cases results in better erectile function outcomes after RP (Ju et al., 2021). Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively (Salonia et al., 2012). The recovery

time following surgery is of clinical importance in terms of postoperative recovery of erectile function. Available data confirm that post-operative erectile function recovery can occur up to 48 months after RP. (Glickman et al., 2009) Likewise, it has been suggested that post-operative therapy (any type) should be commenced as soon as possible after the surgical procedure, (Salonia et al., 2012; Sanda et al., 2008) although evidence suggests that the number of patients reporting the return of spontaneous erectile function has not increased. In terms of the effects of surgical interventions (e.g., robot-assisted RP [RARP] vs. other types of surgery), data are still conflicting. An early systematic review showed a significant advantage in favour of RARP in comparison with open retropubic RP in terms of 12-month potency rates, (Novara et al., 2012) without significant differences between laparoscopic RP and RARP. Some recent reports confirm that the probability of erectile function recovery is about twice as high for RARP compared with open RP (Stolzenburg et al., 2015). More recently, a prospective, controlled, non-randomised trial of patients undergoing RP in 14 Swedish centres comparing RARP versus open retropubic RP, showed a small improvement in erectile function after RARP (Haglind et al., 2015). Conversely, a randomised controlled phase 3 study of men assigned to open RP or RARP showed that the two techniques yielded similar functional outcomes at 12 weeks (Yaxley et al., 2016). More controlled prospective well-designed studies, with longer follow-ups, are necessary to determine if RARP is superior to open RP in terms of post-operative ED rates (Isgoren et al., 2014).To overcome the problem of heterogeneity in the assessment of erectile function, for which there is variability in terms of the PROMs used (e.g., International Index of Erectile Function [IIEF], IIEF-5, Expanded Prostate Cancer Index Composite with 26 items [EPIC 26], Sexual Health Inventory for Men, etc.) to measure potency or erectile function, the criteria used to define restoration of erectile function should be re-evaluated utilising objective and validated thresholds (e.g., normalisation of scores or

return to baseline erectile function) (Capogrosso et al., 2020). ED is also a common problem after both external beam radiation therapy (EBRT) and brachytherapy for PCa. A systematic review and meta-analysis including men treated with EBRT (65%), brachytherapy (31%) or both (4%) showed that the post-treatment prevalence of ED was 34% at 1 year and 57% at 5.5 years (Gaither et al., 2017; Stember & Mulhall, 2012). Similar findings have been reported for stereotactic radiotherapy with 26-55% of previously sexually functioning patients reporting ED at 5 years (Loi et al., 2019). Recently other modalities have emerged as potential therapeutic options in patients with clinically localised PCa, including whole gland and focal (lesion-targeted) treatments, to ablate tumours selectively while limiting sexual toxicity by sparing the neurovascular bundles. These include high-intensity focused US (HIFU), cryo-therapeutic ablation of the prostate (cryotherapy), focal padeliporfin-based vascular-targeted photodynamic therapy and focal radiation therapy (RT) by brachytherapy or CyberKnife ®. All these approaches have a less-negative impact on erectile function with many studies reporting a complete recovery at a one-year follow-up (Fallara et al., 2021). However, prospective randomised controlled studies are needed to compare the functional and oncological outcomes using different treatment modalities (Valerio et al., 2017; van der Poel et al., 2018).

3. Management of erectile dysfunction

3.1 Patient education - consultation and referrals

Educational intervention often represents the first approach to treat ED. It consists of informing patients on psychological and physiological processes subtending sexual response, discussing the expectations and needs of the patients and their sexual partner. It should also review the patient's and partner's understanding of ED, the results of diagnostic tests, and provide a rationale for treatment selection (Francesco Montorsi et al., 2010). This first-level approach prompts sexual satisfaction in ED patients (Frühauf et al., 2013). Patient and partner education is an essential part of ED management, (Hatzichristou et al., 2010; Francesco Montorsi et al., 2010) and may prevent misleading information that can be responsible for dysfunctional psychological processes underpinning ED.

3.2 Treatment options

Currently, available evidence proposed a novel comprehensive therapeutic and decision-making algorithm for ED treatment (Fig. 6).

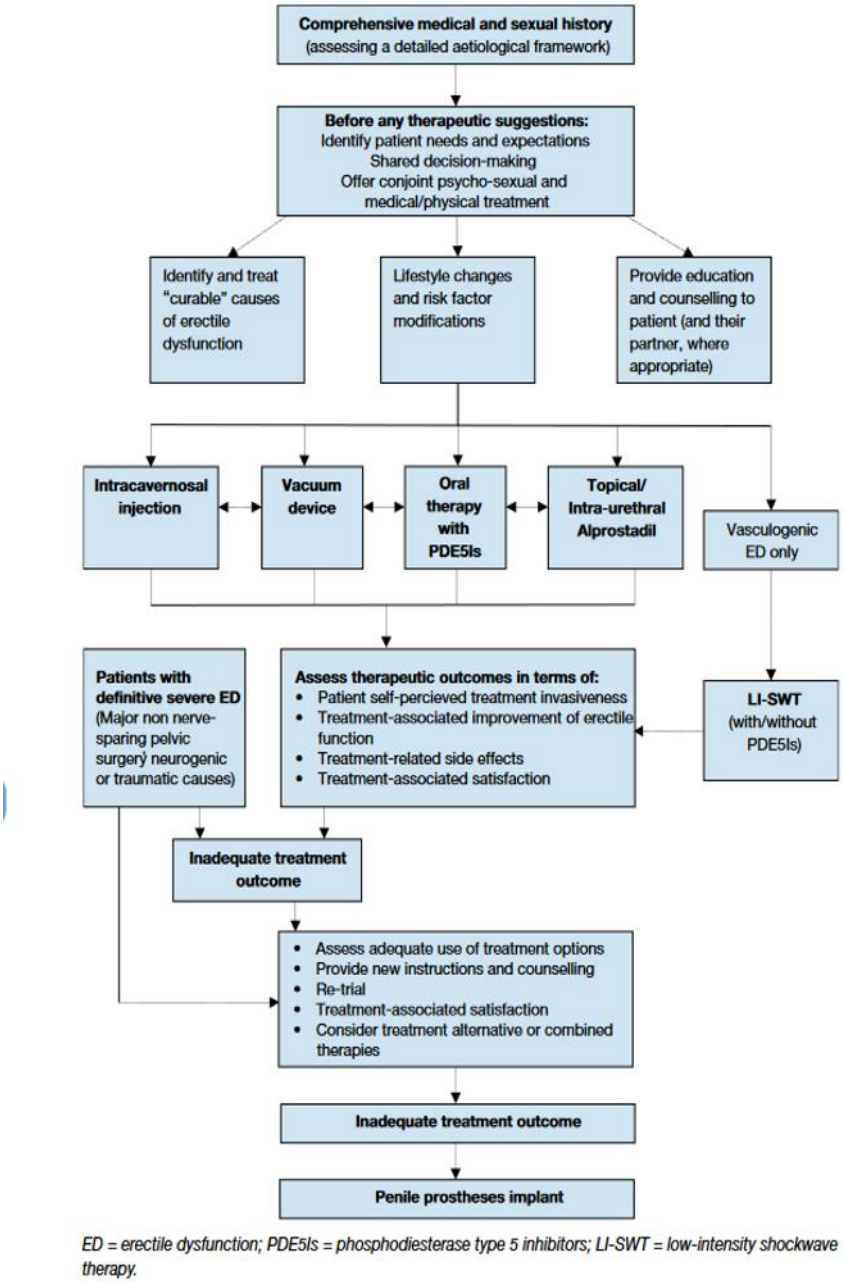

Figure 6: Management algorithm for erectile dysfunction (Capogrosso et al., 2022)

This newly developed treatment algorithm better tailor a personalised therapy, according to the invasiveness, tolerability and effectiveness of the different therapeutic options and patients' expectations. ED may be associated with modifiable or reversible risk factors, including lifestyle ones (Gupta et al., 2011). These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (e.g., endocrine disorders and metabolic disorders such as diabetes, and some cardiovascular diseases such as hypertension) which should always be well-controlled as the first step of any ED treatment (Hatzimouratidis et al., 2016). Several clinical potential benefits of lifestyle changes may be achieved in men with CV or metabolic disorders, such as diabetes or hypertension (Gupta et al., 2011; Moyad et al., 2004). ED can be treated successfully with current treatment options, but it cannot be cured, except for psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g., hypogonadism) (Andrea M Isidori et al., 2014; Mario Maggi et al., 2013). Most men with ED are not treated with cause-specific therapeutic options. This results in a tailored treatment strategy that depends on invasiveness, efficacy, safety and cost, as well as patient preference (Francesco Montorsi et al., 2010). In this context, physician-patient (partner, if available) dialogue is essential throughout ED management. Interesting insights come from a recent systematic review that showed a consistent discontinuation rate for all available treatment options (4.4-76% for PDE5Is); 18.6-79.9% for intracavernous injections; 32-69.2% for urethral suppositories; and 30% for penile prostheses). Men's beliefs about ED treatment, therapeutic ineffectiveness, adverse effects, quality of men's intimate relationships and treatment costs are the most prevalent barriers to treatment actual use (Williams et al., 2021).

3.2.1 Oral pharmacotherapy

Four potent selective PDE5 inhibitors (PDE5Is) have been approved by EMA for ED treatment (Table 1) (JinQiu Yuan et al., 2013).

Table 1- Properties of available phosphodiesterase type 5 inhibitors

Drug name	**Trade name (company)**	**Peak absorption post ingestion (hours)**	**Serum half-life (hours)**	**Take on empty stomach?**
Sildenafil [*]	Viagra (Pfizer)	1–2	3–5	Yes
Vardenafil [*]	Levitra (GlaxoSmithKline)	1–2	3–5	Yes
Tadalafil	Cialis (Lilly)	2–4	18	No
Avanafil	Stendra (Mitsubishi Tanabe)	0.5	6	No

[*]Consider taking 1–2 hours prior to a meal.

PDE5Is have been beneficial in correcting ED in a wide range of patients with varying aetiologies of sexual dysfunction. Sildenafil has been shown to improve erections, leading to successful intercourse in 63% of men with ED compared with 29% of men using a placebo. A study in 2001 showed that 59% of patients with type 2 diabetes mellitus were (Permpongkosol et al., 2016) able to have successful intercourse while taking sildenafil compared with only 14% of those using a placebo (Debruyne et al., 2017). In hypogonadal patients who have not responded to treatment with PDE5 inhibitors alone, recent studies have suggested that a combination of testosterone supplementation and a PDE5 inhibitor can improve erectogenic outcomes (Rastrelli et al., 2016). In men with PCa who have undergone nerve-sparing radical prostatectomy, erectile function declines while the caver-

nous nerves recover from the surgical trauma. Although data regarding the efficacy of penile rehabilitation in radical prostatectomy patients are mixed, the design of studies outside of the Pfizer-sponsored sildenafil study (Calof et al., 2005) is fraught with significant methodological limitations. Thus, so far, no study has defined the exact role of PDE5Is in penile rehabilitation in this patient population. Of note, one randomized placebo-controlled trial in men who have undergone radiotherapy for PCa has demonstrated greater preservation of sexual function in those treated with PDE5Is versus a placebo (P. Boyle et al., 2016). Since they are not initiators of erection, PDE5Is require sexual stimulation to facilitate an erection. Efficacy is defined as an erection, with rigidity sufficient for satisfactory intercourse (Eardley et al., 2010).

To date, the comparison of the most widely available PDE5Is (i.e., sildenafil, tadalafil, vardenafil, and avanafil) in terms of efficacy and/ or patient preference has not been performed in double- or triple-blind multicentre studies. Drug choice depends on intercourse frequency (occasional use or regular therapy, 3-4 times weekly) and patient's personal experience. Two different network meta-analyses demonstrated that ED patients who prioritise high efficacy must use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg and switch to Udenafil 100 mg if the treatment is not sufficient (however, Udenafil 100 mg is not EMA or US Food and Drug Administration approved and is not available in Europe) (L. Chen et al., 2015; Madeira et al., 2021). The results of another clinical trial have revealed that tadalafil 5 mg once daily may improve erectile function among men who have a partial response to on-demand PDE5I therapy (Burns et al., 2015).

In animal studies, it has been demonstrated that the chronic use of PDE5Is significantly improves or prevents the intracavernous structural alterations caused by age, diabetes or surgical damage (Behr-Roussel et al., 2005; M G Ferrini et al., 2007; Monica G Ferrini,

Davila, et al., 2006; Kovanecz et al., 2008; Vignozzi et al., 2006). An RCT has shown that there is no clinically beneficial effect on endothelial dysfunction measured by flow-mediated dilation with a daily tadalafil administration when compared to a placebo (Brock et al., 2016). In 2007, tadalafil 2.5 and 5 mg/day have been approved by EMA for ED treatment. Tadalafil, 5 mg once daily, is well-tolerated, effective, and provides an alternative to on-demand tadalafil for couples preferring spontaneous rather than scheduled sexual activities (Hartmut Porst et al., 2014). Moreover, there is no clinically significant difference between a tadalafil treatment administered continuously (once daily) vs. on-demand regimen (Brock et al., 2016). The appropriateness of the continuous use of a daily regimen should be reassessed periodically (Buvat et al., 2014; Hartmut Porst et al., 2014).

Safety issues for PDE5Is

(i) Cardiovascular safety

Several studies on patients receiving PDE5Is have demonstrated no increase in myocardial infarction rates. In addition, PDE5Is do not have an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina (Kloner et al., 2018; JinQiu Yuan et al., 2013). Both chronic and on-demand use of PDE5Is is well-tolerated with a similar safety profile. However, PDE5Is should be prescribed according to the 3rd Princeton Consensus Panel recommendations in patients with CVD or in those with high CV risk (Ajay Nehra et al., 2012). Co-administration of PDE5Is with antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) can result in small additive decreases in blood pressure (Ajay Nehra et al., 2012). However, the adverse event profile of PDE5Is is not worsened by antihypertensive administration (Pickering et al., 2004).

(ii) Contraindication for the PDE5Is use

An absolute contraindication to PDE5Is is the use of any form of organic nitrate (e.g., nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or NO donors (e.g., other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate such as "poppers" that are used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 hours if sildenafil (and probably also vardenafil) is used (half-life, 4 hours), or at least 48 hours if tadalafil is used (half-life, 17.5 hours), and for no less than 12 hours if avanafil is used (half-life, 6-17 hours) (G Corona et al., 2008; Gur et al., 2013; Kloner, 2004; Pickering et al., 2004; Swearingen et al., 2013). In addition, the concurrent use of PDE5Is and nicorandil is contraindicated. Nicorandil, a potassium channel opener, can promote vasorelaxation by increasing cyclic GMP levels (Satake et al., 1995). A possible explanation is the nitric oxide donating properties of nicorandil.

(iii) PDE5I interaction with α-Blocker interactions

Currently, Tadalafil 5 mg is the only licensed drug for both ED and lower urinary tract symptoms (LUTS) treatment showing an overall good efficacy in relieving urinary symptoms and improving erectile function (Gacci et al., 2016). Therefore, Tadalafil should be considered in patients with mild to moderate LUTS associated with ED either alone or in combination with alpha-blockers. However, considering that both drugs are vasodilators with a potential risk of hypotension, historically there has always been caution in the combination of alpha-blockers and PDE5I (any) because of the fear of possible cumulative effects on blood pressure, based on the evidence from some individual studies that reported the tolerability of combination therapy. (Adamou et al., 2020; Capogrosso et al., 2017; Moncada et al., 2004) However, a recent meta-analysis concluded that concomitant treatment with α-blockers [both non-uroselective (e.g., terazosin and doxazosin) and uro-selective (e.g., alfuzosin, tamsulosin and silodosin) and PDE5Is may produce changes in haemodynamic parameters, but it does not increase the rate of adverse events due to hypotension (Satake et al., 1995).

Management of non-responders to PDE5Is

Two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy (McCullough et al., 2002). The management of non-responders depends upon identifying the underlying cause (Hatzichristou et al., 2005).

The most common causes of incorrect drug use are:

i) failure to use adequate sexual stimulation. PDE5I action is dependent on the NO release by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the medication is ineffective. Furthermore, the reduced production of NO that occurs in diabetic patients due to peripheral neuropathy is thought to be the justification for the higher failure rate of PDE5Is in this category of patients;

ii) failure to use an adequate dose. There is a large counterfeit market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication;

iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse. Oral PDE5Is take different times to reach maximal plasma concentrations (Cmax) (Debruyne et al., 2011; Forgue et al., 2006; Moncada et al., 2004; Nichols et al., 2002; Raymond C Rosen et al., 2004; Tsertsvadze et al., 2009; H. Wang et al., 2014). Although pharmacological activity is achieved at plasma levels below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all four drugs have an onset of action in some patients within 15-30 minutes of oral ingestion, (Debruyne et al., 2011; Forgue et al., 2006; Nichols et al., 2002; Raymond C Rosen et al., 2004; Tsertsvadze et al., 2009) most patients require a longer delay between taking the medication (Eric Chung & Broc, 2011; Francesco Montorsi, Padma-Nathan, et al., 2004; H Padma-Nathan et al., 2003; H. Wang et al., 2014). Absorption of both sildenafil and vardenafil can be delayed by a heavy, fatty meal (Rajagopalan et al., 2003). Absorption of tada-

lafil is less affected, and food has negligible effects on its bioavailability (Forgue et al., 2006). When avanafil is taken with a high-fat meal, the rate of absorption is reduced with a mean delay in Tmax of 1.25 hours and a mean reduction in Cmax of 39% (200 mg) (Kyle et al., 2013; H. Wang et al., 2014; R. Wang et al., 2012). It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is ~4 hours, suggesting that the normal window of efficacy is 6-8 hours following drug ingestion, although responses following this time period are recognised. The half-life of avanafil is 6-17 hours. Tadalafil has a longer half-life of ~17.5 hours, so the window of efficacy is longer at ~36 hours. Data from uncontrolled studies suggest that patient education can help salvage an apparent non-responder to a PDE5I (Gruenwald et al., 2006; Hatzichristou et al., 2005; Park et al., 2013a, 2013b; Hartmut Porst et al., 2013). After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I (Gruenwald et al., 2006; Hatzichristou et al., 2005; Park et al., 2013b). A systematic review has addressed the association between genetic polymorphism, especially those encoding endothelial nitric oxide synthase, and the variability in response to PDE5Is (Mostafa et al., 2020). Similar recent data have suggested that response to sildenafil treatment is also dependent on polymorphism in the PDE5A gene, which encodes the principal cGMP-catalysing enzyme in the penis, regulating cGMP clearance, and it is the primary target of sildenafil (Azevedo et al., 2017; Lacchini et al., 2018; Marchal-Escalona et al., 2016).

3.2.2 Topical/Intraurethral alprostadil

The vasoactive agent alprostadil administration can be performed intraurethrally using a cream that includes a permeation enhancer to facilitate absorption of alprostadil (200 and 300 μg) via the urethral meatus (Anaissie & Hellstrom, 2016; Rooney et al., 2009). Although clinical evidence is still limited, the treatment significantly improves the outcome in mild-to-severe ED patients (Harin Padma-Nathan & Yeager, 2006). In addition, alprostadil efficacy can be increased by direct delivery within the urethral meatus (Cai et al., 2019). Adverse effects of topical alprostadil include penile erythema, penile burning, and pain that usually resolve within 2 hours of application. Systemic adverse effects are rare. The second delivery method is by intra-urethral insertion of a specific formulation of alprostadil (125-1000 μg- initial recommended dose 500 μg) in a medicated pellet (MUSE™) (Suarez-Ibarrola et al., 2020). Erections sufficient for intercourse are achieved in 30-65.9% of patients (Costa & Potempa, 2012; J P Mulhall et al., 2001; H Padma-Nathan et al., 1997). The application of a constriction ring at the root of the penis may improve efficacy (Costa & Potempa, 2012; J P Mulhall et al., 2001). The most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration. Efficacy rates are significantly lower than for intracavernous pharmacotherapy, (Shabsigh et al., 2000) with ~30% adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

3.2.3 Shockwave therapy

In the last decade, LI-shockwave therapy (SWT) has been increasingly proposed as a treatment for vasculogenic ED, being the only available option that might offer a cure that represents the most desired outcome for ED patients (Capogrosso, Frey, et al., 2019; Eric Chung & Cartmill, 2015; Fode et al., 2017; Gruenwald et al., 2012, 2013; Hisasue et al., 2016; Kitrey et al., 2016; Olsen et al., 2015; Yoram Vardi et al., 2010). LI-SWT has shown a beneficial effect on patient-reported erectile function in several single-arm trials. However, data from prospective randomised trials are conflicting, especially because of the heterogeneity among shockwave generators (i.e., electrohydraulic, electromagnetic, piezoelectric and electro-pneumatic); type of shockwaves delivered (i.e., focused, linear, semi-focused and unfocused); set-up parameters (e.g., energy flux density and number of pulses per session) and treatment protocols (i.e., duration of treatment, number of sessions per week, total number of shockwave pulses delivered and penile sites of application) (Hartmut Porst, 2021; Sokolakis & Hatzichristodoulou, 2019). In a recent trial trying to assess the best treatment parameters, no significant differences were observed between various energy flux density levels although a 0.10 mJ/mm^2 seems to perform slightly better than lower energies (Kalyvianakis & Hatzichristou, 2017). Several studies have suggested that LI-SWT can significantly improve the outcome in mild vasculogenic ED patients. However, the improvement appears modest and the rates of patients reporting a satisfactory improvement range between 40-80% (Capogrosso, Frey, et al., 2019; Sokolakis & Hatzichristodoulou, 2019). Few studies have shown an improvement in penile haemodynamic parameters after LI-SWT, but the clinical meaning of this improvement remains unclear (Kalyvianakis & Hatzichristou, 2017; Sokolakis & Hatzichristodoulou, 2019). Likewise, LI-SWT could ameliorate erection quality also in severe ED patients either PDE5Is nonre-

sponders (Amado Bechara et al., 2016; Kitrey et al., 2016; Vinay et al., 2021) or inadequate responders (Lu et al., 2017). The treatment effect is evident starting from 1-3 months after treatment completion, with a subsequent progressive decrease of the achieved benefit in terms of erectile function over time, although some effects could be still detected up to 5 years after treatment (Eric Chung & Cartmill, 2021; Kalyvianakis & Hatzichristou, 2017; Sokolakis & Hatzichristodoulou, 2019). Recently, the LI-SWT impact has been also tested for penile rehabilitation after radical prostatectomy in two randomised trials showing only a modest advantage compared to conventional PDE5Is (Baccaglini et al., 2020; Ladegaard et al., 2021). Large prospective RCTs and long-term follow-up studies are needed to assess the LI-SWT effectiveness for ED and to define the correct treatment protocols (Campbell et al., 2019; Fojecki et al., 2017).

3.2.4 Psychosocial intervention and therapy

Different psychosocial approaches including sexual skills training, marital therapy, psychosexual education (Frühauf et al., 2013) and Cognitive and Behavioural Therapy (CBT - group or couple format), are recommended to treat dysfunctional cognitive and behavioural patterns influencing ED (Brotto et al., 2016). In particular, several CBT techniques aim to identify triggers responsible for erectile difficulties, restructure dysfunctional thinking styles, learn coping skills to deal with erectile difficulties and emotional symptoms, improve communication skills with the partner, and relapse prevention. The CBT approach combined with medical treatment for ED is considered an optimal procedure (Dewitte et al., 2021). Moreover, there is preliminary evidence supporting the role of mindfulness-based therapy for ED and associated outcomes (Bossio et al., 2018).

3.2.5 Hormonal treatment

Both primary testicular failure and secondary pituitary/hypothalamic causes (e.g., a functional pituitary tumour resulting in hyperprolactinaemia) result in testosterone deficiency (Maggi et al., 2013; Tajar et al., 2012).

Men with low or low-normal testosterone levels and related sexual desire, erectile function and sex-life dissatisfaction, when clinically indicated, can be treated with testosterone therapy (intramuscular, transdermal, or oral) (Rizk et al., 2017).

3.2.6 Vacuum erection devices

Corpus cavernosum engorgement can be passively achieved with vacuum erection device (VED) with a constrictor ring placed at the penis base to retain blood within the corpus. The efficacy of this strategy on erections satisfactory for intercourse is as high as 90%, and satisfaction rates range between 27% and 94%. Pain, inability to ejaculate, petechiae, bruising, and numbness represent the most common adverse events (J Yuan et al., 2010). VED is contraindicated in patients with bleeding disorders or on anticoagulant therapy (Lewis & Witherington, 1997; Trost et al., 2016). VED can be recommended in well-informed older patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED (L A Levine & Dimitriou, 2001; Pajovic et al., 2017; J Yuan et al., 2010).

3.2.7 Intracavernous injections therapy

The first medical treatment of ED was the intracavernous administration of vasoactive drugs (Eardley et al., 2010; Hartmut Porst et al., 2013). These vasoactive agents injected directly into the corpora cavernosa via a small needle, include prostaglandin E1, papaverine and phentolamine (and sometimes atropine), which work alone or in combination to

elicit an erection. The intracavernous injections show a high success rate (85%) (Coombs et al., 2012; Shabsigh et al., 2000).

Current available drugs, that can be used alone or in combination, taking advantage of the different modes of action as well as alleviating adverse effects by using lower concentrations of each drug, are:

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy because of its high incidence of adverse effects as monotherapy. Papaverine is currently not licensed for the treatment of ED.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for the intracavernous treatment of ED. Intracavernous alprostadil is most efficacious as monotherapy at a dose of 5-40 μg (40 μg may be offered off-label in some European countries). The erection appears after 5-15 minutes and lasts according to the dose injected, but with significant heterogeneity among patients. Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED population, as well as in patient subgroups (e.g., men with diabetes or CVD), with reported satisfaction rates of 87-93.5% in patients and 86-90.3% in partners after the injections (Eardley et al., 2010; Hartmut Porst et al., 2013). Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), excessively prolonged undesired erections (5%), priapism (1%), and fibrosis (2%) (Eardley et al., 2010; Lakin et al., 1990; Hartmut Porst et al., 2013). Pain is usually self-limited after prolonged use and it can be alleviated with the addition of sodium bicarbonate or local anaesthesia (Eardley et al., 2010; Moriel & Rajfer, 1993; Hartmut Porst et al.,

2013). Cavernosal fibrosis (from a small haematoma) usually clears within a few months after the temporary discontinuation of the injection programme. However, tunical fibrosis suggests the early onset of Peyronie's disease and may indicate stopping intracavernous injections indefinitely. Systemic adverse effects are uncommon. The most common is mild hypotension, especially when using higher doses. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders. Despite these favourable data, drop-out rates of 41-68% have been reported for intracavernous pharmacotherapy, (Eardley et al., 2010; Hartmut Porst et al., 2013; Ruchira Gupta, Jill Kirschen, Robert C. Barrow, n.d.; Sundaram et al., 1997) with most dropouts occurring within the first 2-3 three months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy, of 10% per year. Reasons for discontinuation included desire for a permanent mode of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%) (Duncan et al., 2019; H Porst et al., 1998; Y Vardi et al., 2000).

Other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide, are usually combined with the main drugs (Buvat et al., 1998; J P Mulhall et al., 1997). However, most combinations are not standardized formulations and show a limited availability worldwide. The current available intracavernous injection therapies based on the combination of different drugs are:

- Bimix, Trimix: papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg) (also known as Bimix), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 μg) (also known as Trimix), have been widely used with improved efficacy rates, although they have never been licensed for ED (A Bechara et al., 1997; Meinhardt et al., 1994). Trimix has the highest efficacy rates, reaching 92%; this combination has similar adverse effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on the total dose).
- Invicorp™: Vasoactive intestinal peptide (25 μg) plus phentolamine mesylate (1-2 mg Invicorp), currently licensed in Scandinavia, is a combination of two active components with complementary modes of action.

Several clinical studies have revealed that the drug combination is effective for intracavernous injections in > 80% of men with ED, including non-responders to other therapies and shows a low incidence of penile pain and a trascurable priapism risk (Dinsmore & Wyllie, 2008). The combination of intracavernous injections has no effects in 5-10% of patients. The sildenafil combination with intracavernous injection of the triple combination regimen may rescue as many as 31% of patients who do not respond to the triple combination alone (McMahon et al., 1999). However, combination therapy is related to an increased incidence of side effects in 33% of patients. This strategy can be considered in seleted patients before proceeding to a penile implant.

3.2.8 Novel therapies for ED

Currently, innovative vasoactive agents, trophic factors, stem cell therapy and gene therapy have been proposed as potential novel strategies for ED treatment. Among trophic factors, intracavernous injection of platelet-rich plasma (PRP) has been recently investigated in several prospective and retrospective trials (Banno et al., n.d.; Chalyj et al., 2015; M. Epifanova et al., 2020; Matz et al., 2018; Poulios et al., 2021). The regenerative PRP effect is deemed to be exerted through growth factors such as VEGF, EGF, IGF-1, PDGF and FGF that are the highly concentrated into the platelets. These factors may be responsible for angiogenesis stimulation and stem cell recruitment (Oudelaar et al., 2019). In addition, stem cell therapy has been recently proposed as a promising approach for restorative ED treatment (Lokeshwar et al., 2020). Further investigation in large-scale, blinded, placebo-controlled randomised studies are strongly needed to achieve adequate evidence-based and clinically-reliable recommendation grades (Maya V Epifanova et al., 2020; J. H. Kim et al., 2016; Matz et al., 2019; D. P. Patel et al., 2019; Scott et al., 2019; Yu et al., 2018). Pre-clinical studies have shown a neuro-regenerative effect and an improved penile vascular-risation in both cavernous nerve injury and diabetic rat-model (Alkandari et al., 2022). To date, several clinical trials, one randomised placebo controlled-trial, (Poulios et al., 2021) two prospective randomised trials, (Chalyj et al., 2015) two prospective cohorts (M. Epifa-nova et al., 2020; Oudelaar et al., 2019) and two retrospective studies (Banno et al., n.d.; Matz et al., 2018) demonstrated favourable outcomes of PRP injections for ED treatment (Alkandari et al., 2022). In the only randomised placebo-controlled trial, 60 patients with mild to moderate vasculogenic ED were randomised to receive two injections of 10 mL PRP (n=30) or placebo (n=30). (Poulios et al., 2021) At 1, 3 and 6-month follow-ups, the rate of patients reporting an MCID (minimal clinically important differences) improvement

in the IIEF-EF score was significantly higher in the treatment group, with 69% achieving MCID 6 months after PRP compared to 27% in the placebo group ($p < 0.001$). IIEF-EF scores improved by a mean of 2.7 points at 1 month and 3.9 points at 6-month assessment after treatment. Regarding safety, the mean VAS score was higher as compared with the placebo (2.6 vs. 2.2, respectively, $p = 0.008$) but no haemorrhagic events or other side effects were reported (Poulios et al., 2021). Despite these encouraging results, the available evidence is still insufficient to provide a recommendation regarding the use of PRP for ED treatment in clinical practice. Indeed, current studies are limited by the low number of patients included (ranging from 10-100), the lack of placebo comparison (except for 1 small RCT) and the heterogeneity in terms of the modality of PRP preparation. The concentration of platelets and growth factors could vary according to the system used for preparation (Mazzucco et al., 2009) and there is a lack of consensus concerning the optimal platelet concentration as well as the need for combining PRP with activating agents to maximise the growth factors release (Alkandari et al., 2022; Mazzucco et al., 2009).

3.2.9 Surgical management

Oral and vacuum erection treatment represent the first- and second-line management choice for ED patients. However, these therapeutic options often fail, show adverse effects or have contraindications (i.e., ED and penile fibrosis secondary to Peyronie disease; priapism or severe infections; genital or pelvic trauma). Therefore, surgery is the only strategy to treat ED. Penile revascularization and penile prosthesis have been described below.

Penile revascularization

Penis revascularization has been developed to anastomose the inferior epigastric artery to either the deep dorsal vein or the dorsal artery, to increase penile vascular inflow and reduce venous outflow. Currently, this strategy is recommended for young men (<55 years) that are non-smokers, not diabetic, and showing isolated stenosis at the segment of the internal pudendal artery without a concomitant venous leak. In young patients with perineal or pelvic trauma, penile revascularisation has a success rate of 60-70% in the long-term (Sohn et al., 2013; Trost et al., 2016). Corporeal veno-occlusive dysfunction is contraindicated to revascularisation and should be excluded by dynamic infusion cavernosometry or cavernosography.

Penile prostheses

The penile prosthesis implantation is applied for patients that need a definitive therapy, or patients that are not suitable for different drugs or do not respond to pharmacological therapies (Fig. 7) (Antonini et al., 2016).

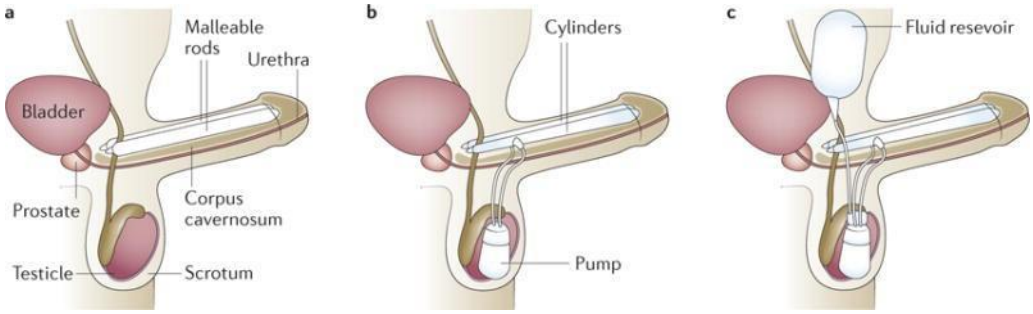

Figure 7: Penile prostheses (Yafi et al., 2016)

Frequently, men treated with penile prosthesis implantation show an organic ED cause, such as diabetes, vascular disease, previous pelvic surgery/trauma and Peyronie's disease (Bajic et al., 2020) (Muneer et al., 2020). The mean duration of ED symptoms before surgical intervention ranges from 3-6 six years (Bajic et al., 2020). Currently, available penile implants are inflatable (two- and three-piece) and semi-rigid devices (malleable, mechanical and soft flexible) (Casabé et al., 2016; Hellstrom et al., 2010; Laurence A Levine et al., 2016; Montague, 2011; Salonia et al., 2012). Semi-rigid prostheses result in a firm penis, that can be manually placed in an erect or flaccid state and offer the advantage of a simple implant technique, as well as easy use for the patient (Hellstrom et al., 2010; Laurence A Levine et al., 2016; Montague, 2011; Salonia et al., 2012). However, an unnatural persistent erection and reduced concealability represent disadvantages (Montague, 2011; John J Mulcahy et al., 2004). Penile prosthesis implantation is performed by two surgical approaches: peno-scrotal and infrapubic (E Chung et al., 2013; Laurence A Levine et al., 2016; Montague, 2011; John J Mulcahy et al., 2004). The peno-scrotal approach has been suggested to provide excellent exposure; afford proximal crural exposure, avoid dorsal nerve injury, and permit direct visualisation of pump placement. However, with this approach, the reservoir is either placed blindly into the retropubic space, which can result in visceral injury in patients with a history of major pelvic surgery (mainly radical cystic-

tomy) or a separate incision in the abdomen is placed under direct vision. A recent systematic review comparing the satisfaction and complication rates of the different surgical approaches has shown that there is no specific advantage between the two, but rather it is recommended that surgeons have knowledge of both techniques and are capable of tailoring the incision strategy for complex cases (Palmisano et al., 2018). Revision surgery is associated with poorer outcomes and may be more challenging. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED with appropriate counselling. (Chierigo et al., 2019; E Chung et al., 2013; Dewitte et al., 2021; Falcone et al., 2013; Hellstrom et al., 2010; Henry, Brinkman, et al., 2012; Laurence A Levine et al., 2016; Lux et al., 2007; Natali et al., 2008; Otero et al., 2017; Salonia et al., 2012) In patients with favourable oncological prognosis after RP for PCa, the penile prosthesis implantation to treat ED, and a male sling or artificial urinary sphincter implantation to hold stress urinary incontinence is effective and durable (Hellstrom et al., 2010; Lee et al., 2011, 2013; Salonia et al., 2012; Segal et al., 2013). After penile implant surgery, sexuality and sexual well-being can be improved by psychosexual counselling in both patients and partners (Pisano et al., 2015). Infection and mechanical failure represent the main penile prosthesis implantation complications. Technical improvement of the commonly employed prostheses (e.g., AMS 700CX/CXR™ and Titan Zero degree™) resulted in a mechanical failure rate of < 5% 5 years of follow-up (C. C. Carson et al., 2000; Hellstrom et al., 2010; Wilson et al., 1999).

In the last few decades, several pieces of evidence suggests that the penile prosthesis risk of infection has reduced with device improvement and surgical expertise (Christodoulidou & Pearce, 2016). A reduction of the infection rates to 2-3% can be reached by careful surgical techniques with appropriate antibiotic prophylaxis against both Gram-positive and

Gram-negative bacteria in low-risk patients (Eric Chung et al., 2018; Mahon et al., 2020; Mandava et al., 2012; Trost et al., 2013). A further reduction of the infection rate to 1-2% can be obtained by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) (C. C. 3rd Carson et al., 2011; Darouiche et al., 2013; Mandava et al., 2012; Serefoglu et al., 2012; Zargaroff et al., 2014). Additionally, infection risk can be further decreased by using coated prostheses, performing prolonged post-operative antibiotics (> 24 hours), treating the skin with chlorhexidine alcohol, and applying surgical techniques that avoid prolonged wound exposure and reduce skin contact (i.e., no-touch technique) (Dropkin & Kaufman, 2021; Pineda & Burnett, 2016). Identification and pre-treatment of patients who are colonised with nasal Staphylococcus aureus with mupirocin and chlorhexidine prior to surgery have been shown to reduce the incidence of postoperative surgical site infection from 4.4% to 0.9% in a placebo-controlled randomised trial (Bode et al., 2010). Higher-risk patients include those undergoing revision surgery, or with impaired host defences (immunosuppression, diabetes mellitus, or spinal cord injury) or with penile corporal fibrosis (Hatzimouratidis et al., 2012; Hellstrom et al., 2010; Henry, Donatucci, et al., 2012; Laurence A Levine et al., 2016; Laurence A Levine & Burnett, 2013; Trost et al., 2013). Diabetes mellitus is a relevant risk factor for penile prostheses infection. It is debated if lowering this risk by optimising glycaemic control before surgery or excluding diabetic patients from penile prostheses implantation (Lipsky et al., 2019). Unfortunately, there are no RCTs determining the ideal and/or correct threshold of glycated haemoglobin that is acceptable prior to implant surgery in diabetic patients (Canguven et al., 2018). Recently, it has been demonstrated that vancomycin + gentamicin treatment of men with diabetes who received a Coloplast Titan™ implant is effective to prevent postoperative infection and subsequent explantation and revision (Cihan et al., 2009; Towe et al., 2020). Infection requires removal of the pro-

sthesis and antibiotic administration. Alternatively, removal of the infected device with immediate salvage and replacement with a new prosthesis has been described using a wash-out protocol with successful salvages achieved in > 80% of cases (Gross et al., 2016; Henry, Donatucci, et al., 2012; J J Mulcahy, 2000; Trost et al., 2013). The majority of revisions are secondary to mechanical failure and combined erosion or infection (Pineda & Burnett, 2016; Serefoglu et al., 2012). Ninety-three percent of cases are successfully revised, providing functioning penile prosthesis (C. C. 3rd Carson et al., 2011; Habous et al., 2016; Laurence A Levine et al., 2016; Serefoglu et al., 2012; Trost et al., 2013).

There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rate (Akakpo et al., 2017). However, there are no studies comparing the different manufacturers' implants, demonstrating the superiority of one implant type over others (Atri et al., 2020).

4. Exploring the relationship between obstructive sleep apnoea and erectile dysfunction: a cross sectional clinical study

Obstructive Sleep Apnoea (OSA) is a frequent disease caused by episodes of partial or total airway obstruction during the sleep resulting in hypoxia, poor sleep quality and narcolepsy. Over 100 million people are estimated to be affected worldwide, with a prevalence in the range of 9-38% (Benjafield et al., 2019; Y. Zhang et al., 2019). OSA is capable to exert a profoundly negative effect on the quality of life (Stepnowsky et al., 2019; İrer et al., 2018; Silva et al., 2016), and it is also associated with obesity, increasing age, and male gender (Gabbay & Lavie, 2012; Hull et al., 1999; Jehan et al., 2017, 2018). Furthermore, patients with OSA are frequently diagnosed with diabetes, hypertension, cardiovascular diseases, and sexual dysfunctions (Bonsignore et al., 2019; Pinto et al., 2016; Zheng et al., 2020). Although OSA cannot be included among the well-established causes of ED, conclusive evidence indicates that patients with OSA are at higher risk of ED (Manfredi et al, 2022; C.-M. Chen et al., 2015; Hoyos et al., 2015; Kellesarian et al., 2018; Romero-Otero et al., 2021; Sperlongano et al., 2014), while it is noteworthy that treatment with continuous positive airway pressure (CPAP) is associated with an improved erectile function (Li et al., 2010; Pascual et al., 2018). The exact pathogenic mechanisms that make patients with OSA at higher risk of sexual dysfunctions remain elusive, although several hypotheses have been made (Kalejaiye et al., 2017) (Hoyos et al., 2015). Comorbidities that are prevalent both in patients with ED and OSA, such as diabetes, hypertension and metabolic syndrome, may contribute to the onset of both conditions, e.g., by increasing systemic inflammation levels and causing vascular damage (Bouloukaki et al., 2014; Hoyos et al., 2015; Kellesarian et al., 2018). Decreased nocturnal erections during the rapid eye movement (REM) periods, increased adrenergic tone and hormonal imbalances can also contri-

bute to ED pathogenesis in OSA patients (Andersen et al., 2010). Patients at higher risk of OSA can be identified using several validated questionnaires such as the Berlin questionnaire (BQ), STOP-Bang questionnaire and the Epworth Sleepiness Scale (ESS) (Amra et al., 2018; Pereira et al., 2013). Polysomnography (PSG) represents the gold standard for the diagnosis of OSA, but it is expensive, time-consuming and available only in referral centers (Gregório et al., 2011). On this basis, overnight ambulatory respiratory polygraphy (RP) is more commonly used, as it only requires a portable monitoring and recording device, which makes it possible to use it at home (Berry et al., 2012).

This clinical study was conceived to assess the prevalence and evaluate the clinical characteristics of ED in a cohort of patients with a diagnosis of OSA. We also explored the relationship between polygraphic and endoscopy parameters, with erectile function scores, with the intent to gather evidence regarding the etiopathogenetic links between ED and OSA.

4.1 Methods

This prospective observational study was approved by the Research Ethics Board of the University of Naples "Federico II" (n. 316/20) and conducted in accordance with the Declaration of Helsinki Guidelines. Informed consent was obtained from all patients. We evaluated 133 consecutive male patients complaining of snoring, sleepiness, morning dry mouth, and tiredness compatible with OSA between January 2018 and November 2019 (Y. Zhang et al., 2019). We excluded patients under the age of 18; those with psychiatric, neurological, hepatic, pulmonary, oncological, or endocrinological diseases (other than diabetes); and those with previous diagnosis and treatment for ED. This study excluded also patients with cardiovascular diseases due to their association with ED (Terentes-Printzios et al., 2022). Furthermore, patients with chronic liver disease were excluded due to an altered hypothalamic-pituitary-gonadal axis, which may influence erectile function (Burra et al., 2010). Full medical history, complete ear nose and throat evaluation and sexual hormonal assessment (serum total testosterone (T), prolactin (PRL), luteinizing hormone (LH), and follicle-stimulating hormone (FSH)) were obtained from all subjects at the time of the enrolment in the study. C-reactive protein (CRP), albumin, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol and triglycerides were assessed as well. We measured the height and weight of all patients, calculating their Body Mass Index (BMI) based on weight (Kg)/height (m). The Epworth Sleepiness Scale (ESS) and the 5-International Index of Erectile Function (IIEF-5) questionnaires were then administered to patients. An eight-item questionnaire, the ESS (range 0-24), assesses the likelihood of falling asleep under different circumstances, with a cut-off of ≥10 points indicating excessive daytime sleepiness (Trimmel et al., 2018; Vignatelli et al., 2003). International Index of Erectile Function (IIEF) 5 is an abridged five-item version of the 15-item

International Index of Erectile Function, designed to assess erectile function over the previous four weeks. Erectile dysfunction is indicated by a score of 21 (D'Elia et al., 2012; R.C. Rosen et al., 1999).

All subjects underwent overnight ambulatory RP (Weinmann SOM-NOlab 2, Hamburg, Germany) in accordance with the American Academy of Sleep Medicine Guidelines (Berry et al., 2012). Electrocardiogram, thoracic and abdominal excursion, oral and nasal airflow by thermistor, breath sounds, body position, and oxygen saturation by pulse oximeter were all recorded. Our evaluations included the Apnea-Hypopnea Index (AHI), Oxygen Desaturation Index (ODI), the frequency of events per night, mean arterial blood oxygen saturation (SaO2), and sleep time below 90% SaO2 (SatO2-nadir). Berry et al. (2012) determined apnoea severity based on AHI values: mild (AHI 5–15), moderate (AHI 16–30) or severe (AHI >30). At RP, an AHI greater than 5 was diagnosed as OSA. Successively, drug-induced sleep endoscopy (DISE) was performed, in order to evaluate potential surgical treatment candidates and clinical mismatches. DISE was performed employing a flexible rhinopharyngolaryngoscope (Storz, Tuttlingen, Germany) in the operating theatre using a propofol target-controlled infusion (TCI) to achieve a complete evaluation of the upper airways (UA) collapse. Bispectral Index (BIS) was used to check the level of sedation during DISE. Blinded VOTE classification scoring was used for classifying the type of obstruction detected at DISE. The VOTE classification represents a method to assess the type of obstruction, based on the collapse and closure of the airway of different oropharyngeal structures (velum, oropharynx, tongue base, epiglottis) (Kezirian et al., 2011).

IBM SPSS software was used for statistical analysis (version 25, IBM Corp, Armonk, NY, USA). Continuous variables were described as means and standard deviations, while categorical variables were described as frequencies and percentages. The Kolmogorov–Smirnov test and parametric tests were used to determine whether the data were normal. In

order to assess sample size, a power analysis was conducted based on the assumption that 50% of OSA patients have erectile dysfunction, according to alpha = 0.005 and beta = 0.2 (Feng et al., 2022; Rosner, 2015). In relation to IIEF-5, every variable was correlated using Pearson's correlation coefficient. To compare continuous variables between patients with and without ED, an independent-sample t-test was performed, while a Chi-Square test was performed for categorical variables. IIEF-5 scores were compared using a two-way ANOVA. The IIEF-5 score was then predicted using univariate and multivariate linear regression based on variables that showed statistically significant correlations. A p-value of 0.05 was considered significant.

4.2 Results

According to polygraphic parameters, 80 male patients with OSA met the inclusion criteria and were enrolled (Figure 1).

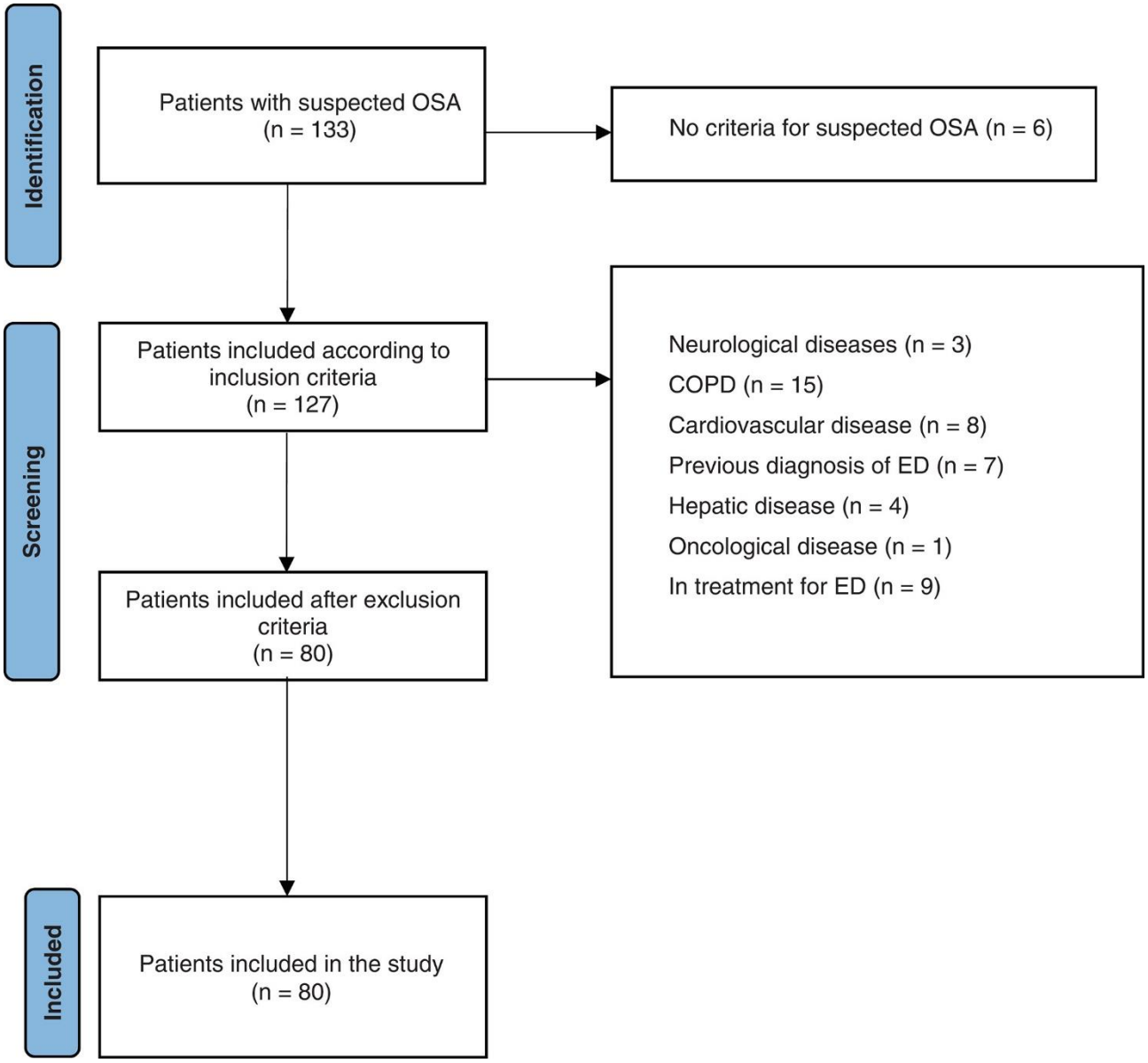

Figure 1 Patients included in the study. COPD, chronic obstructive pulmonary disease; ED, Erectile dysfunction; OSA, obstructive sleep apnoea

16 (20%) patients presented a mild OSA (AHI 5–15),35 (44%) a moderate OSA (AHI 15–30), and 29 (36%) a severe OSA (AHI >30). 60% of patients (48/80), based on IIEF-5 ≤21 (mean score 18.15 ± 5.63 SD), were diagnosed with ED. Laboratory data and RP parameters are reported in Table 1.

	Mean	Standard Deviation
Age	54,99	9,2
BMI	27,03	3,33
ESS	8,13	4,66
IIEF-5	18,15	5,63
AHI/h	27,63	15,05
ODI	22,68	11,54
SaO_2-nadir (%)	85,60	3,86
Total Colesterol (mg/mL)	194,75	32,56
LDL (mg/mL)	120,66	29,30
HDL (mg/mL)	46,71	7,79
Triglycerides (mg/dL)	135,78	37,62
Albumin (mg/dL)	4,46	0,62
Testosterone (ng/dL)	564,26	143,94
PRL (ng/mL)	11,68	4,53
FSH (mIU/mL)	5,43	2,99
LH (mIU/mL)	6,55	3,09
PCR (mg/L)	3,73	2,32
	Yes	No
Hypertension (%)	33 (41.3)	47 (58.8)
Diabetes (%)	12 (15)	68 (85)
Smoking (%)	21 (26.3)	59 (73.8)
	Mean	Std. Deviation
Pack/year	36,95	17,47

TABLE 1 Descriptive characteristics

Abbreviations: AHI, Apnea-Hypopnea Index; BMI, body mass index; CRP, C-reactive protein; ESS, Epworth Sleepiness Scale; FSH, follicle-stimulating hormone; HDL, high density lipoproteins; IIEF-5, 5-International Index of Erectile Function; LDL, low density lipoproteins; LH, luteinizing hormone; ODI, Oxygen Desaturation Index; PRL, prolattin; SaO2, oxygen saturation.

A statistically significant correlation was reported between IIEF-5 and age, hypertension, diabetes, ESS, AHI, ODI and SaO2-nadir, reporting, in particular, an inverse correlation between OSA parameters and IIEF-5 (Figure 2).

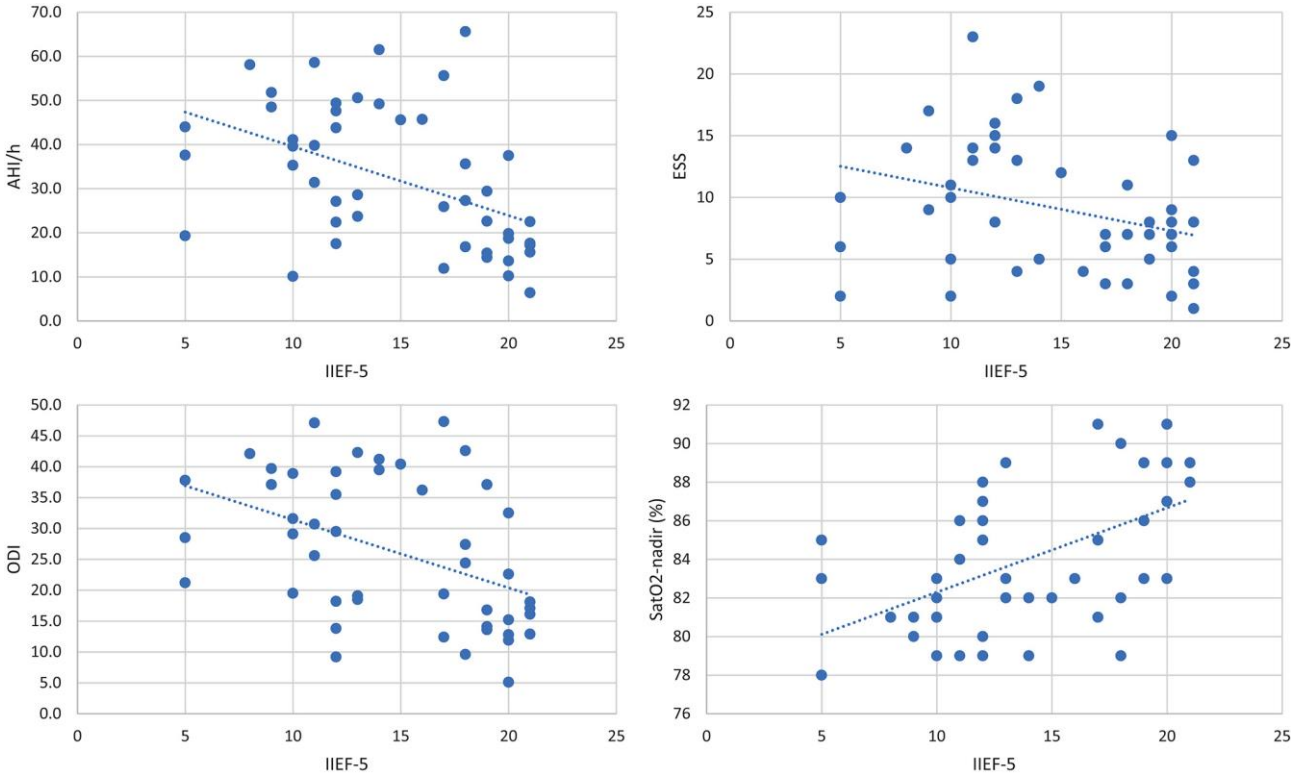

Figure 2: Scatter plots of IIEF-5 and OSA parameters obtained via linear regression.

AHI/h and IIEF-5) r2 = 0.218, p = 0.001; ESS and IIEF-5) r2 = 0.103, p = 0.026; ODI and IIEF-5) r2 = 0.200, p = 0.001; Sat02-nadir (%) and IIEF-5) r2 = 0.218, p = 0.001; r2 = 0.200, p = 0.001. ESS, Epworth Sleepiness Scale; ODI, Oxygen Desaturation Index; OSA, obstructive sleep apnoea

ANOVA analysis showed no statistically significant differences between VOTE patterns and IIEF-5 scores (V patterns, p = 0.397; O patterns, p = 0.413; T patterns, p = 0.433; E patterns, p = 0.322). In a multiple linear regression analysis, age, diabetes, and SaO2-nadir were significantly associated with IIEF-5 (Table 2).

UNIVARIATE ANALYSIS			
	r	r^2	P
Age	-0.415	0.17	**<0.0001**
Hypertension	-0.327	0.11	**0.003**
Diabetes	-0.412	0.17	**<0.0001**
Smoking	0.147	0.02	0.194
BMI	-0.214	0.045	0.057
ESS	-0.375	0.14	**0.001**
AHI	-0.524	0.27	**<0.0001**
ODI	-0.516	0.26	**<0.0001**
$SatO_2$-nadir	0.569	0.32	**<0.0001**
Cholesterol	0.134	0.01	0.237
LDL	0.125	0.01	0.268
HDL	0.146	0.02	0.196
Triglycerides	-0.059	0.003	0.605
Albumin	-0.217	0.047	0.053
Testosterone	0.131	0.017	0.247
PRL	0.020	0.0004	0.860
FSH	-0.174	0.03	0.122
LH	-0.025	0.0006	0.825
PCR	0.176	0.031	0.119

MULTIVARIATE ANALYSIS				
	Beta Coefficient	95% C.I		P
Age	-0.164	-0.279	-0.05	**0.006**
Hypertension	-0.702	-2.928	1.524	0.532
Diabetes	-3.332	-6.373	-0.291	**0.032**
ESS	-0.210	-0.454	0.034	0.091
AHI	0.022	-0.14	0.184	0.789
ODI	-0.027	-0.225	0.170	0.784
$SatO_2$-nadir	0.558	0.149	0.967	**0.008**

TABLE 2. Univariate and multivariate linear regression between parameters and IIEF-5

Abbreviations: AHI, Apnea-Hypopnea Index; BMI, body mass index; CRP, C-reactive protein; ESS, Epworth Sleepiness Scale; FSH, follicle-stimulating hormone; HDL, high density lipoproteins; IIEF-5, 5-International Index of Erectile Function; LDL, low density lipoproteins; LH, luteinizing hormone; ODI, Oxygen Desaturation Index; PRL, prolattin; SaO2, oxygen saturation. Bold indicates statistically significant P < 0.05.

Among 48 emergency department patients with mild ED (IIEF-5 scores of 17–21), 27.1% mild to moderate ED (IIEF-5 scores of 12–16), 20.8% moderate ED (IIEF-5 scores: 8–11), and 6.3% severe ED (IIEF-5 scores: 5–7), according to the study. There was a significant difference in the main EES score between patients with an ED and those without an ED ($t(77.71) = -2.646$; $p = 0.010$). The mean AHI score in ED subjects was 32.1 ± 16 whereas in non-ED subjects was 24.5 ± 12.8 [$t(77.9) = —3.767$; $p < 0.0001$]; with analogous results for ODI [26.17 ± 11.8 vs. 17.43 ± 8.99 with $t(76.5) = —3.754$; $p < 0.0001$] and SaO2-nadir (%) [84.38 ± 3.8 vs. 87.44 ± 3.19 $t (73.9) = 3.749$; $p < 0.0001$]. Also, the average age of ED and non-ED patients was significantly different [$t(78) = -3.801$; p 0.0001]. We found normal testosterone levels in OSA patients with (555.38 ± 150 ng/dl) and without ED (577.59 ± 135 ng/dl). There was no statistically significant difference between the first and second groups, despite lower values reported in the first. Albumin concentrations, however, were statistically significantly different between the two groups [4.6 + 0.62 in ED and 4.26 + 0.57 in OS] non-ED, $t(78) = —2.455$, $p = 0.016$]. ED patients also had a higher prevalence of diabetes [22.9% vs. 8.3% with $X2 (1) = 3.79$, $p = 0.015$] (Table 3).

	No ED		ED		P
	Mean	Std. Deviation	Mean	Std. Deviation	
Age	50.56	7.750	57.94	8.964	**<0.0001**
BMI	26.2253	2.67900	27.5615	3.61751	0.062
Pack/year	31.75	21.519	40.15	14.473	0.296
ESS	6.63	3.240	9.13	5.205	**0.010**
IIEF-5	23.25	1.078	14.75	4.787	**<0.0001**
AHI/h	20.928	10.5065	32.106	16.0328	**<0.0001**
ODI	17.434	8.9935	26.179	11.7972	**<0.0001**
SaO_2-nadir (%)	87.44	3.192	84.38	3.813	**<0.0001**
Col	196.97	35.618	193.27	30.665	0.622
LDL	122.16	31.943	119.67	27.706	0.712
HDL	48.59	8.860	45.46	6.804	0.078
Triglycerides	128.25	35.360	140.79	38.592	0.145
Albumin (mg/dL)	4.263	0.5701	4.600	0.6230	**0.016**
Testosterone (ng/dL)	577.59	135.022	555.38	150.324	0.502
PRL (ng/mL)	11.8700	4.78751	11.5606	4.39693	0.769
FSH (mIU/mL)	4.759	2.9024	5.875	2.9980	0.103
LH (mIU/mL)	6.472	3.1089	6.610	3.1155	0.846
PCR (mg/L)	4.200	2.2606	3.413	2.3319	0.138
	Yes	No	Yes	No	
Hypertension	9 (28.1)	23 (71.9)	24 (50)	24 (50)	0.052
Diabetes	1 (8.3)	31 (96.9)	11 (22.9)	37 (77.1)	**0.015**
Smoking	8 (25)	24 (75)	13 (27.1)	35 (72.9)	0.836

TABLE 3. Differences in parameters in patients with and without ED. Independent sample t-test and Chi square test was performed for continuous and categorical variables respectively

Abbreviations: AHI, Apnea-Hypopnea Index; BMI, body mass index; CRP, C-reactive protein; ED, Erectile dysfunction; ESS, Epworth Sleepiness Scale; FSH, follicle-stimulating hormone; HDL, high density lipoproteins; IIEF-5, 5-International Index of Erectile Function; LDL, low density lipoproteins; LH, luteinizing hormone; ODI, Oxygen Desaturation Index; PRL, prolattin; SaO2, oxygen saturation. Bold indicates statistically significant $P < 0.05$.

4.3 Discussion

Sleep apnea is a common medical condition associated with sleep fragmentation, episodes of hypoxia, and daytime somnolence (Kalejaiye et al., 2017; Zheng et al., 2020). Researchers found that OSA patients with ED had a prevalence of 41% to 80%; interestingly, CPAP treatment improved not only the ED but also possible hormonal deficiencies (Hoyos et al., 2015; Zheng et al., 2020). Likewise, in our sample size, we found that 60% of OSA patients were diagnosed with ED with a mean IIEF-5 value of 18.1 ± 5.6 (SD). Among possible causative factors linking ED and OSA, increased oxidative stress with reduced vasodilation and bioavailability of nitric oxide (NO), an increase in catecholamines and endothelin levels, sleep fragmentation, decreased amounts of REM sleep, daytime sleepiness, impaired vigilance, longer bulbocavernosus reflex latency, and decreased testosterone are among the most important. (Schulz et al., 2019). The literature supports the hypothesis that OSA is associated with low libido and biochemical androgen deficiency, but these relationships are not clearly assessed and are far less recognized (Pascual et al., 2018; Schulz et al., 2019).

In our study population, testosterone levels were normal in the overall cohort as well as in the ED patients. It is possible that this is due to the relatively young age of patients involved in our study. Hypoxia, reduced sleep time, and sleep fragmentation can reduce testosterone levels (Wittert, 2014). Due to the prevalence of obesity among patients with OSA, BMI could play a significant role in determining testosterone levels (Barone, 2022; Shamim et al., 2015). It could be due to the increased expression of aromatase in adipose tissue and the reduction of sex hormone-binding globulin (Colleluori et al., 2020). There is probably no correlation between OSAS and hormonal status in our cohort of patients due to a relatively low BMI. It is however to be noted that the testosterone threshold required

to maintain an erection is relatively low and therefore, the influence of BMI and the expression of adipose-tissue aromatase on erectile dysfunction could only be significant in men with severe cases of hypogonadism (Andrea M Isidori et al., 2014). Participants in our study complained of snoring, sleepiness, morning dry mouth, and fatigue. Over-night ambulatory RP confirmed the diagnosis of OSA. As observed in our study population, most apneic patients were overweight, cigarette smokers, hypertensive, and diabetic type 2 (DM2). In spite of the finding of OSA symptoms in our patients (27.6 ± 15), the ESS score did not show values compatible with OSA (8.1 ± 4.6; Johns, 1991). For a clear diagnosis of OSA, an overnight RP is recommended (Laratta et al., 2017).

In our cohort of 80 OSA patients, 26.3% were smokers, 41% were hypertensive, and 15% were type 2 diabetic. In the literature, there has been no conclusive evidence linking OSA to smoking. Despite some studies suggesting that AHI increases with the smoking rate, this relationship could not be confirmed (Hsu et al., 2019). Similarly to literature reports, 26.3% of OSA patients smoke, which is consistent with our findings which show that 22% of newly diagnosed OSA patients were current/ former smokers. (Shao et al., 2020)

According to recent literature, approximately half of our OSA patients had systemic hypertension. We also found that 15% of patients had DM2 and were overweight (Goldberger et al., 2008). There is probably a multidirectional relationship between OSA, DM2 and obesity. As a result, obesity, increased visceral fat, and leptin and insulin resistance are perpetuating factors for DM2 in patients with OSA (Berger & Polotsky, 2018; Jehan et al., 2018). OSA, when combined with DM2, may affect glycemic control, increasing the risk of DM2 complications (Khaire et al., 2020).

Diabetes prevalence and mean age were higher among ED patients, confirming their role as ED risk factors. In non-ED patients, the ESS score was higher, but still less than 10. Additionally, we found a significant correlation between ESS and RP parameters (AHI,

ODI and SatO2-nadir). The level of albumin in OSA patients with ED was slightly higher in our study. Contrary to different studies in the literature that report a correlation between hypoalbuminemia and ED in chronic hepatitis and cirrhosis patients (Hunter et al., 2014), these results are contrary to these studies. In patients with liver disease, however, the causes of ED are unknown and the disruption of vascular, hormonal, and neurological integrity may result in an increased and independent risk for sexual dysfunction (M. Kim et al., 2015). Hypoalbuminemia could also explain ED in patients with altered ratios of free and albumin-bound testosterone. These premises make our controversial data regarding albumin level an interesting topic for discussion. Further research is needed to evaluate the clinical significance of this finding.

This is the first study to correlate ED parameters with DISE evaluation. Despite inconclusive data regarding ED and DISE, our data indicated that ED correlated with OSA regardless of VOTE patterns, which, however, are subject to subjective interpretation. Further, we demonstrated that OSA severity affected erectile function, with a negative correlation between OSA parameters (AHI, ESS, and O2 Saturation Nadir) and IIEF-5. The results of multiple logistic regression showed that age, diabetes, and SaO2-nadir were independent predictors of IIEF-5 and ED ($p = 0.001$, $p = 0.001$, $p = 0.037$, respectively). We found that IIEF-5 scores decreased by 0.164 points per year of age, and by 3.33 points per year of diabetes, but improved by 0.558 points per 1% increase in SatO2-nadir, based on our model. Despite the relatively small sample size, this study found that treating and preventing diabetes is crucial to preventing ED, especially in patients with OSA, where diabetes is a major comorbidity associated with the ineffectiveness of PDE5-I therapy. (Garrido-Abad et al., 2022). It is also possible to improve ED by improving oxygenation through CPAP treatment, oral appliances, or surgery following OSA treatment. The study has several limitations. Firstly, the study design is prone to sampling bias. Secondly, RP

and DISE assessments were performed by different operators, even though they were conducted in the same clinic. Lastly, the IIEF-5 and the ESS assessment are subjective questionnaires with wide intervariability; fourth, despite being similar to other studies in the literature, our sample size is still too small to evaluate the influence of DISE patterns in ED. These limitations necessitate a cautious evaluation of the results obtained.

4.5 Conclusions

This study revealed that among the non endocrine factors affecting ED, OSA displays an emerging role. Our results emphasize the relevance of OSA screening in patients that undergo investigations for ED, and vice versa, cosidering the high ED prevalence among OSA patients. Accordingly, several measurements could be used for the identification of OSA patients at higher risk for ED. In our study we pointed out that OSA parameters correlate with ED and age, whereas SatO2-nadir and diabetes are independent predictors of ED. We found that men with OSA who attend the Ear, Nose, and Throat (ENT) clinic are at significant risk of developing ED. In conclusion, although several therapeutic approaches have been proposed but with a limited improvement of ED, as CPAP treatment, novel therapeutic approaches are strongly needed for a tailored precision medicine to overcome ED. The CPAP treatment could be combined with other therapeutic options, such as weight reduction or sildenafil, depending on ED severity. However, the improvement in patient awareness of both OSA and ED could reduce the drop out frequently observed in therapy and consequently could be useful for achieving a better treatment adherence.

5. References

1. Adamou C., Ntasiotis P., Athanasopoulos A. and Kallidonis P. (2020). **The hemodynamic interactions of combination therapy with α-blockers and phosphordiesterase-5 inhibitors compared to monotherapy with α-blockers: a systematic review and meta-analysis**. *International Urology and Nephrology*, *52*(8), 1407–1420. https://doi.org/10.1007/s11255-020-02454-6

2. Akakpo W., Pineda M.A. and Burnett A.L. (2017). **Critical Analysis of Satisfaction Assessment After Penile Prosthesis Surgery**. *Sexual Medicine Reviews*, *5*(2), 244–251. https://doi.org/10.1016/j.sxmr.2017.01.001

3. Akakpo W., Pineda M.A. and Burnett A.L. (2017). **Critical Analysis of Satisfaction Assessment After Penile Prosthesis Surgery**. *Sexual Medicine Reviews*, *5*(2), 244–251. https://doi.org/10.1016/j.sxmr.2017.01.001

4. Alkandari M.H., Touma N. and Carrier S. (2022). **Platelet-Rich Plasma Injections for Erectile Dysfunction and Peyronie's Disease: A Systematic Review of Evidence**. *Sexual Medicine Reviews*, *10*(2), 341–352. https://doi.org/10.1016/j.sxmr.2020.12.004

5. Amra B., Rahmati B., Soltaninejad F. and Feizi A. (2018). **Screening Questionnaires for Obstructive Sleep Apnea: An Updated Systematic Review**. *Oman Medical Journal*, *33*(3), 184–192. https://doi.org/10.5001/omj.2018.36

6. Anaissie J. and Hellstrom W.J. (2016). **Clinical use of alprostadil topical cream in patients with erectile dysfunction: a review**. *Research and Reports in Urology*, *8*, 123–131. https://doi.org/10.2147/RRU.S68560

7. Andersen M.L., Santos-Silva R., Bittencourt L. R.A. and Tufik S. (2010). **Prevalence of erectile dysfunction complaints associated with sleep disturbances in Sao Paulo, Brazil: a population-based survey**. *Sleep Medicine*, *11*(10), 1019–1024. https://doi.org/10.1016/j.sleep.2009.08.016

8. Andersson K.E., and Wagner G. (1995). **Physiology of penile erection**. *Physiological Reviews*, *75*(1), 191–236. https://doi.org/10.1152/physrev.1995.75.1.191

9. Andric S.A., Janjic M.M., Stojkov N J. and Kostic T.S. (2010). **Testosterone-induced modulation of nitric oxide-cGMP signaling pathway and androgenesis in the rat Leydig cells**. *Biology of Reproduction*, *83*(3), 434–442. https://doi.org/10.1095/biolreprod.110.083626

10. Antonini G., Busetto G. M., De Berardinis E., Giovannone R., Vicini P., Del Giudice F., Conti S.L., Gentile V. and Perito P.E. (2016). **Minimally invasive infrapubic inflatable penile prosthesis implant for erectile dysfunction: evaluation of efficacy, satisfaction profile and complications**. *International Journal of Impotence Research*, *28*(1), 4–8. https://doi.org/10.1038/ijir.2015.33

11. Arslan D., Aslan G., Sifil A. et al. (2002). **Sexual dysfunction in male patients on emodialysis: assessment with the International Index of Erectile Function (IIEF)**. Int J Impot Res.;14(6):539-542. https://doi:10.1038/sj.ijir.3900937

12. Atri E., Wong V., Barengo N.C., Nieder A.M. and Polackwich A.S. (2020**). A Comparison Between AMS 700 and Coloplast Titan: A Systematic Literature Review**. *Cureus*, *12*(11), e11350. https://doi.org/10.7759/cureus.11350

13. Azevedo A.A.M., Brites-Anselmi G., Pinheiro L.C., de Almeida Belo V., Coeli-Lacchini F.B.F., Molina C.A., de Andrade M.F., Tucci S., Hirsc E., Tanus-Santos J.E., Lacchini R. (2017)**. Relationship between asymmetric dimethylarginine, nitrite and genetic polymorphisms: Impact on erectile dysfunction therapy**. *Nitrix Oxide*, *71*, 44–51. https://doi.org/10.1016/j.niox.2017.10.006

14. Baccaglini W., Pazeto C.L., Corrêa Barros E.A., Timóteo F., Monteiro L., Saad Rached R.Y., Navas A. and Glina S. (2020). **The Role of the Low-Intensity Extracorporeal Shockwave Therapy on Penile Rehabilitation After Radical Prostatectomy: A Randomized Clinical Trial**. *The Journal of Sexual Medicine*, *17*(4), 688694. https://doi.org/10.1016/j.jsxm.2019.12.024

15. Bacon C.G., Mittleman M.A., Kawachi I., Giovannucci E., Glasser D.B. and Rimm E.B. (2006). **A prospective study of risk factors for erectile dysfunction**. *The Journal of Urology*, *176*(1), 217–221. https://doi.org/10.1016/S0022-5347(06)00589-1

16. Bajic P., Mahon J., Faraday M., Sadeghi-Nejad H., Hakim L., and McVary, K.T. (2020). **Etiology of Erectile Dysfunction and Duration of Symptoms in Patients Undergoing Penile Prosthesis: A Systematic Review**. *Sexual Medicine Reviews*, 8(2), 333–337. https://doi.org/10.1016/j.sxmr.2019.05.003

17. Ballard S.A., Gingell C.J., Tang K. et al. (1998). **Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes**. *J Urol.*; 159:2164–2171. https://doi.org/10.1016/S0022-5347(01)63299-3

18. Bancroft J. and Wu F.C. (1983). **Changes in erectile responsiveness during androgen replacement therapy**. *Archives of Sexual Behavior*, *12*(1), 59–66. https://doi.org/10.1007/BF01542116

19. Banno J.J., Kinnick T.R., Roy L., Perito P., Antonini G. and Banno D. (2017.). **The Efficacy of Platelet-Rich Plasma (PRP) as a Supplemental Therapy for the Treatment of Erectile Dysfunction (ED): Initial Outcomes**. *The Journal of Sexual Medicine*, *14*(2), 59–60. https://doi.org/10.1016/j.jsxm.2016.12.134

20. Barone B., Napolitano L., Abate M., Cirillo L., Reccia P., Passaro F., Turco C., Morra S., Mastrangelo F., Scarpato A., Amicuzi U., Morgera V., Romano L., Arcaniolo D. and Felice Crocetto (2022). **The Role of Testosterone in the Elderly: What Do We Know?** *International Journal of Molecular Sciences*, *23*(7). https://doi:10.3390/ijms23073535

21. Basaria S., Harman S.M., Travison T.G., Hodis H., Tsitouras P., Budoff M., Pencina K.M., Vita J., Dzekov C., Mazer N.A., Coviello A.D., Knapp, P.E., Hally K., Pinjic E., Yan, M., Storer T.W. and Bhasin S. (2015). **Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial**. *JAMA*, *314*(6), 570–581. https://doi.org/10.1001/jama.2015.8881

22. Baskin L.S., Sutherland R.S., DiSandro M.J., Hayward S.W., Lipschutz J. and Cunha G.R. (1997). **The effect of testosterone on androgen receptors and human penile growth**. *The Journal of Urology*, *158*(3 Pt 2), 1113–1118. https://doi.org/10.1097/00005392-199709000-00108

23. Bechara A, Casabé A., Chéliz G., Romano S., Rey H. and Fredotovich N. (1997). **Comparative study of papaverine plus phentolamine versus prostaglandin E1 in erectile dysfunction**. *The Journal of Urology*, *157*(6), 2132–2134. https://doi.org/10.1016/S0022-5347(01)64694-9

24. Bechara Amado, Casabé A., De Bonis W. and Ciciclia P.G. (2016). **Twelve-Month Efficacy and Safety of Low-Intensity Shockwave Therapy for Erectile Dysfunction in Patients Who Do Not Respond to Phosphodiesterase Type 5 Inhibitors**. *Sexual Medicine*, *4*(4), e225–e232. https://doi.org/10.1016/j.esxm.2016.06.001

25. Behr-Roussel D., Gorny D., Mevel K., Caisey S., Bernabé J., Burgess G., Wayman C., Alexandre L. and Giuliano F. (2005). **Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: lack of tachyphylaxis**. *European Urology*, *47*(1), 87–91. https://doi.org/10.1016/j.eururo.2004.09.005

26. Benjafield A.V, Ayas N.T., Eastwood P.R., Heinzer R., Ip M.S.M., Morrell M.J., Nunez C.M., Patel S.R., Penzel T., Pépin J.L., Peppard P.E., Sinha S., Tufik S., Valentine K. and Malhotra A. (2019). **Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis**. *The Lancet. Respiratory Medicine*, *7*(8), 687–698. https://doi.org/10.1016/S2213-2600(19)30198-5

27. Berger S. and Polotsky V.Y. (2018). **Leptin and Leptin Resistance in the Pathogenesis of Obstructive Sleep Apnea: A Possible Link to Oxidative Stress and Cardiovascular Complications**. *Oxidative Medicine and Cellular Longevity*, *2018*, 5137947. https://doi.org/10.1155/2018/5137947

28. Berry R.B., Budhiraja R., Gottlieb D.J., Gozal D., Iber C., Kapur V K., Marcus C.L., Mehra R., Parthasarathy S., Quan S.F., Redline S., Strohl K.P., Davidson Ward S.L. and Tangredi M.M. (2012). **Rules for scoring respiretory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine**. *Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine*, *8*(5), 597–619. .https://doi.org/10.5664/jcsm.2172

29. Bielicki P., Trojnar A., Sobieraj P. and Wąsik M. (2019). **Smoking status in relation to obstructive sleep apnea severity (OSA) and cardiovascular comorbidity in patients with newly diagnosed OSA**. *Advances in Respiratory Medicine*, *87*(2), 103–109. https://doi.org/10.5603/ARM.a2019.0011

30. Blumenthal S.A. (2012). **Earl Sutherland (1915–1974) [corrected] and the discovery of cyclic AMP.** *Perspect Biol Med.*; 55:236–249. https://doi:10.1353/pbm.2012.0017

31. Boas M., Boisen K.A., Virtanen H.E., Kaleva M., Suomi A.M., Schmidt I.M., Damgaard I.N., Kai C.M., Chellakooty M., Skakkebaek N. E., Toppari, J. and Main K.M. (2006). **Postnatal penile length and growth rate correlate to serum testosterone levels: a longitudinal study of 1962 normal boys**. *European Journal of Endocrinology*, *154*(1), 125–129. https://doi.org/10.1530/eje.1.02066

32. Bode L. G.M., Kluytmans J.A.J.W. Wertheim H.F.L. Bogaers D., Vandenbroucke-Grauls C.M.J.E., Roosendaal R., Troelstra A., Box A.T.A., Voss A., van der Tweel I., van Belkum A., Verbrugh H.A. and Vos M.C. (2010). **Preventing surgical-site infections in nasal carriers of Staphylococcus aureus**. *The New England Journal of Medicine*, *362*(1), 9–17. https://doi.org/10.1056/NEJMoa0808939

33. Bonsignore M.R., Baiamonte P., Mazzuca E., Castrogiovanni A. and Marrone O. (2019). **Obstructive sleep apnea and comorbidities: a dangerous liaison**. *Multidisciplinary Respiratory Medicine*, 14(1), 8. https://doi.org/10.1186/s40248-019-0172-9

34. Bossio J.A., Basson R., Driscoll M., Correia S. and Brotto L.A. (2018). **Mindfulness-Based Group Therapy for Men With Situational Erectile Dysfunction: A Mixed-Methods Feasibility Analysis and Pilot Study**. *The Journal of Sexual Medicine*, *15*(10), 1478–1490. https://doi.org/10.1016/j.jsxm.2018.08.013

35. Bouloukaki I., Papadimitriou V., Sofras F., Mermigkis C., Moniaki V., Siafakas N.M. and Schiza S.E. (2014). **Abnormal Cytokine Profile in Patients with Obstructive Sleep Apnea-Hypopnea Syndrome and Erectile Dysfunction**. *Mediators of Inflammation*, *2014*, 568951. https://doi.org/10.1155/2014/568951

36. Boyle H.J., Alibhai S., Decoster L., Efstathiou E., Fizazi K., Mottet N., Oudard S., Payne H., Prentice M., Puts M., Aapro M. and Droz J.P. (2019). **Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients**. *European Journal of Cancer (Oxford, England : 1990)*, *116*, 116–136. https://doi.org/10.1016/j.ejca.2019.04.031

37. Boyle P., Koechlin A., Bota M., d'Onofrio A., Zaridze D.G., Perrin P., Fitzpatrick J., Burnett A.L. and Boniol M. (2016). **Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis**. *BJU International*, *118*(5), 731–741. https://doi.org/10.1111/bju.13417

38. Brackett N.L., Lynne C.M., Ibrahim E., Ohl D.A. and Sønksen J. (2010). **Treatment of infertility in men with spinal cord injury**. *Nature Reviews. Urology*, *7*(3), 162–172. https://doi.org/10.1038/nrurol.2010.7

39. Braun M., Wassmer G., Klotz T., Reifenrath B., Mathers M. and Engelmann U. (2000). **Epidemiology of erectile dysfunction: results of the "Cologne Male Survey"**. *International Journal of Impotence Research*, *12*(6), 305–311. https://doi.org/10.1038/sj.ijir.3900622

40. Brock G., Ni X., Oelke M., Mulhall J., Rosenberg M., Seftel A., D'Souza D. and Barry J. (2016). **Efficacy of Continuous Dosing of Tadalafil Once Daily vs Tadalafil On Demand in Clinical Subgroups of Men With Erectile Dysfunction: A Descriptive Comparison Using the Integrated Tadalafil Databases**. *The Journal of Sexual Medicine*, *13*(5), 860–875. https://doi.org/10.1016/j.jsxm.2016.02.171

41. Brotto L., Atallah S., Johnson-Agbakwu C., Rosenbaum T., Abdo C., Byers E.S., Graham C., Nobre P. and Wylie K. (2016). **Psychological and Interpersonal Dimensions of Sexual Function and Dysfunction**. *The Journal of Sexual Medicine*, *13*(4), 538–571. https://doi.org/10.1016/j.jsxm.2016.01.019

42. Buena F., Swerdloff R.S., Steiner B.S., Lutchmansingh P., Peterson M.A., Pandian M.R., Galmarini M. and Bhasin S. (1993). **Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range**. *Fertility and Sterility*, *59*(5), 1118–1123. https://doi.org/10.1016/S0015-0282(16)55938-X

43. Burns P.R., Rosen R.C., Dunn M., Baygani S.K. and Perelman M.A. (2015). **Treatment satisfaction of men and partners following switch from on-demand phosphodiesterase type 5 inhibitor therapy to tadalafil 5 mg once daily**. *The Journal of Sexual Medicine*, *12*(3), 720–727. https://doi.org/10.1111/jsm.12818

44. Burra P., Germani G., Masier A., De Martin E., Gambato M., Salonia A., Bo P., Vitale A., Cillo U., Russo F.P. and Senzolo M. (2010). **Sexual dysfunction in chronic liver disease: is liver transplantation an effective cure?** *Transplantation*, *89*(12), 1425–1429. https://doi.org/10.1097/TP.0b013e3181e1f1f6

45. Buvat J., Costa P., Morlier D., Lecocq B., Stegmann B. and Albrecht D. (1998). **Double-blind multicenter study comparing alprostadil alpha-cyclodextrin with moxisylyte chlorhydrate in patients with chronic erectile dysfunction**. *The Journal of Urology*, *159*(1), 116-119. https://doi.org/10.1016/s0022-5347(01)64030-8

46. Buvat J., Hatzichristou D., Boess F.G., Büttner H., Gehchan N., Henneges C. and Porst H. (2014). **Continuation and effectiveness of tadalafil once daily during a 6-month observational study in erectile dysfunction: the EDATE study**. *International Journal of Clinical Practice*, *68*(9), 1087–1099. https://doi.org/10.1111/ijcp.12449

47. Cai T., Palumbo F., Liguori G., Mondaini N., Scroppo F.I., Di Trapani D., Cocci A., Zucchi A., Verze P., Salonia A. and Palmieri A. (2019). **The intra-meatal application of alprostadil cream (Vitaros®) improves drug efficacy and patient's satisfaction: results from a randomized, two-administration route, crossover clinical trial**. *International Journal of Impotence Research*, *31*(2), 119–125. https://doi.org/10.1038/s41443-018-0087-6

48. Calof O.M., Singh A.B., Lee M.L., Kenny A.M., Urban R.J., Tenover J.L. and Bhasin S. (2005). **Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials**. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *60*(11), 1451–1457. https://doi.org/10.1093/gerona/60.11.1451

49. Campbell J.D., Trock B.J., Oppenheim A.R., Anusionwu I., Gor R.A. and Bunett A.L. (2019). **Meta-analysis of randomized controlled trials that assess the efficacy of low-intensity shockwave therapy for the treatment of erectile dysfunction**. *Therapeutic Advances in Urology*, *11*, 1756287219838364. https://doi.org/10.1177/1756287219838364

50. Canguven O., Talib R., El Ansari W., Khalafalla K. and Al Ansari A. (2018). **Is Hba1c level of diabetic patients associated with penile prosthesis implantation infections?** *The Aging Male: The Official Journal of the International Society for the Study of the Aging Male*, 1–6. https://doi.org/10.1080/13685538.2018.1448059

51. Capogrosso P., Colicchia M., Ventimiglia E., Castagna G., Clementi M.C., Suardi N., Castiglione F., Briganti A., Cantiello F., Damiano R., Montorsi F. and Salonia A. (2013). **One patient out of four with newly diagnosed erectile dysfunction is a young man--worrisome picture from the everyday clinical practice**. *The Journal of Sexual Medicine*, *10*(7), 1833–1841. https://doi.org/10.1111/jsm.12179

52. Capogrosso P., Frey A., Jensen C.F. S., Rastrelli G., Russo G.I., Torremade J., Albersen M., Gruenwald I., Reisman Y. and Corona, G. (2019). **Low-Intensity Shock Wave Therapy in Sexual Medicine-Clinical Recommendations from the European Society of Sexual Medicine (ESSM)**. *The Journal of Sexual Medicine*, *16*(10), 1490–1505. https://doi.org/10.1016/j.jsxm.2019.07.016

53. Capogrosso P., Pozzi E.P., Celentano V., Sanchez-Salas R. and Salonia A. (2020). **Erectile Recovery After Radical Pelvic Surgery: Methodological Challenges and Recommendations for Data Reporting**. *The Journal of Sexual Medicine*, *17*(1), 7–16. https://doi.org/10.1016/j.jsxm.2019.09.013

54. Capogrosso P., Ventimiglia E., Boeri L., Serino A., Russo A., La Croce G., Capitanio U., Dehò F., Montorsi F. and Salonia A. (2017). **Time of onset of vardenafil orodispersible tablet in a real-life setting - looking beyond randomized clinical trials**. *Expert Review of Clinical Pharmacology*, *10*(3), 339–344. https://doi.org/10.1080/17512433.2017.1288567

55. Capogrosso P., Vertosick E.A., Benfante N.E., Eastham J.A., Scardin P.J., Vickers A.J. and Mulhall J.P. (2019). **Are We Improving Erectile Function Recovery After Radical Prostatectomy? Analysis of Patients Treated over the Last Decade**. *European Urology*, *75*(2), 221–228. https://doi.org/10.1016/j.eururo.2018.08.039

56. Stepnowsky C., Sarmiento K.F., Bujanover S., Villa K.F., Li V.W., Flores N.M. (2019). **Comorbidities, Health-Related Quality of Life, and Work Productivity Among People With Obstructive Sleep Apnea With Excessive Sleepiness: Findings From the 2016 US National Health and Wellness Survey**. *Journal of Clinical Sleep Medicine*, *15*(2). https://doi.org/10.5664/jcsm.7624

57. Carson C.C. 3rd, Mulcahy J.J. and Harsch M.R. (2011). **Long-term infection outcomes after original antibiotic impregnated inflatable penile prosthesis implants: up to 7.7 years of followup**. *The Journal of Urology*, *185*(2), 614–618. https://doi.org/10.1016/j.juro.2010.09.094

58. Carson C.C., Mulcahy J.J. and Govier F.E. (2000). **Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. AMS 700CX Study Group**. *The Journal of Urology*, *164*(2), 376–380. https://doi.org/10.1016/S0022-5347(05)67364-8

59. Casabé A.R., Sarotto N., Gutierrez C. and Bechara A.J. (2016). **Satisfaction assessment with malleable prosthetic implant of Spectra (AMS) and Genesis (Coloplast) models**. *International Journal of Impotence Research*, *28*(6), 228–233. https://doi.org/10.1038/ijir.2016.33

60. Celentano V., Cohen R., Warusavitarne J., Faiz O. and Chand M. (2017). **Sexual dysfunction following rectal cancer surgery**. *International Journal of Colorectal Disease*, *32*(11), 1523-1530. https://doi.org/10.1007/s00384-017-2826-4

61. Chalyj M.E., Grigorjan V.A., Epifanova M.V. and Krasnov A.O. (2015). **The effectiveness of intracavernous autologous platelet-rich plasma in the treatment of erectile dysfunction**. *Urologiia*, *4*, 76–79.

62. Chen C.M., Tsai M.J., Wei P.J., Su Y.C., Yang C.J., Wu M.N., Hsu C.Y., Hwang S.J., Chong I.W. and Huang M.S. (2015). **Erectile Dysfunction in Patients with Sleep Apnea--A Nationwide Population-Based Study**. *PloS One*, *10*(7), e0132510. https://doi.org/10.1371/journal.pone.0132510

63. Chen L., Staubli S.E.L., Schneider M.P., Kessels A.G., Ivic S., Bachmann L.M. and Kessler T.M. (2015). **Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: a trade-off network metaanalysis**. *European Urology*, *68*(4), 674–680. https://doi.org/10.1016/j.eururo.2015.03.031

64. Chierigo F., Capogrosso P., Dehò F., Pozzi E., Schifano N., Belladelli F., Montorsi F. and Salonia A. (2019). **Long-Term Follow-Up After Penile Prosthesis Implantation-Survival and Quality of Life Outcomes**. *The Journal of Sexual Medicine*, *16*(11), 1827–1833. https://doi.org/10.1016/j.jsxm.2019.08.001

65. Christodoulidou M. and Pearce I. (2016). **Infection of Penile Prostheses in Patients with Diabetes Mellitus**. *Surgical Infections*, *17*(1), 2–8. https://doi.org/10.1089/sur.2015.164

66. Chung E., Van C.T., Wilson I. and Cartmill R.A. (2013). **Penile prosthesis implantation for the treatment for male erectile dysfunction: clinical outcomes and lessons learnt after 955 procedures**. *World Journal of Urology*, *31*(3), 591–595. https://doi.org/10.1007/s00345-012-0859-4

67. Chung E. and Broc G.B. (2011). **A state of art review on vardenafil in men with erectile dysfunction and associated underlying diseases**. *Expert Opinion on Pharmacotherapy*, *12*(8), 1341–1348. https://doi.org/10.1517/14656566.2011.584064

68. Chung E. and Cartmill R. (2015). **Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial**. *BJU International*, *115 Suppl*, 46–49. https://doi.org/10.1111/bju.13035

69. Chung E. and Cartmill R. (2021). **Evaluation of Long-Term Clinical Outcomes and Patient Satisfaction Rate Following Low Intensity Shock Wave Therapy in Men With Erectile Dysfunction: A Minimum 5-Year Follow-Up on a Prospective Open-Label Single-Arm Clinical Study**. *Sexual Medicine*, *9*(4), 100384. https://doi.org/10.1016/j.esxm.2021.100384

70. Chung E., Wang R., Ralph D., Levine L. and Brock G. (2018). **A Worldwide Survey on Peyronie's Disease Surgical Practice Patterns Among Surgeons**. *The Journal of Sexual Medicine*, 15(4), 568–575. https://doi.org/10.1016/j.jsxm.2018.01.025

71. Ciacci C., De Rosa A., De Michele G. et al. (1998). **Sexual behaviour in untreated and treated coeliac patients.** *Eur J Gastroenterol Hepatol;* 10(8): 649-651.

72. Cihan A., Demir O., Demir T., Aslan G., Comlekci A. and Esen A. (2009). **The relationship between premature ejaculation and hyperthyroidism**. *The Journal of Urology*, *181*(3), 1273–1280. https://doi.org/10.1016/j.juro.2008.10.150

73. Colleluori G., Chen R., Turin C.G., Vigevano F., Qualls C., Johnson B., Mediwala S., Villareal D.T. and Armamento-Villareal R. (2020). **Aromatase Inhibitors Plus Weight Loss Improves the Hormonal Profile of Obese Hypogonadal Men Without Causing Major Side Effects**. *Frontiers in Endocrinology*, *11*, 277. https://doi.org/10.3389/fendo.2020.00277

74. Coombs P.G., Heck M., Guhring P., Narus J. and Mulhall J.P. (2012). **A review of outcomes of an intracavernosal injection therapy programme**. *BJU International*, *110*(11), 1787–1791. https://doi.org/10.1111/j.1464-410X.2012.11080.x

75. Corona G., Lee D.M., Forti G., O'Connor D.B., Maggi M., O'Neill T.W., Pendleton N., Bartfai G., Boonen S., Casanueva F.F., Finn J.D., Giwercman A., Han T.S., Huhtaniemi I.T., Kula K., Lean M.E.J., Punab M., Silman A.J., Vanderschueren D. and Wu F.C.W. (2010). **Age-related changes in general and sexual health in middle-aged and older men: results from the European Male Ageing Study (EMAS)**. *The Journal of Sexual Medicine*, *7*(4 Pt 1), 1362–1380. https://doi.org/10.1111/j.1743-6109.2009.01601.x

76. Corona G, Razzoli E., Forti G. and Maggi M. (2008). **The use of phosphordiesterase 5 inhibitors with concomitant medications**. *Journal of Endocrinological Investigation*, *31*(9), 799–808. https://doi.org/10.1007/BF03349261

77. Corona G., Isidori A.M., Buvat J., Aversa A., Rastrelli G., Hackett G., Rochira V., Sforza A., Lenzi A., Mannucci E. and Maggi, M. (2014). **Testosterone supplementation and sexual function: a meta-analysis study**. *The Journal of Sexual Medicine*, *11*(6), 1577–1592. https://doi.org/10.1111/jsm.12536

78. Costa P. and Potempa A.J. (2012). **Intraurethral alprostadil for erectile dysfunction: a review of the literature**. *Drugs*, *72*(17), 2243–2254. https://doi.org/10.2165/11641380-000000000-00000

79. D'Elia C., Cerruto M.A., Cavicchioli F.M., Cardarelli S., Molinari A. and Artibani W. (2012). **Critical points in understanding the Italian version of the IIEF 5 questionnaire**. *Archivio Italiano di Urologia, Andrologia: Organo Ufficiale della Societa Italiana di Ecografia Urologica e Nefrologica*, *84*(4), 197-201.

80. Darouiche R.O., Bella A.J., Boone T.B., Brock G., Broderick G.A., Burnett A.L., Carrion R., Carson C. 3rd, Christine B., Dhabuwala C.B., Hakim L.S., Henry G., Jones L.A., Khera M., Montague D.K. and Nehra A. (2013). **North American consensus document on infection of penile prostheses**. *Urology*, *82*(4), 937–942. https://doi.org/10.1016/j.urology.2013.05.048

81. Debruyne F.M. J., Behre H.M., Roehrborn C.G., Maggi M., Wu F.C.W., Schröder F.H., Jones T.H., Porst H., Hackett G., Wheaton O.A., Martin-Morales A., Meuleman E., Cunningham G.R., Divan H.A. and Rosen R.C. (2017). **Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men**. *BJU International*, *119*(2), 216–224. https://doi.org/10.1111/bju.13578

82. Debruyne F.M.J., Gittelman M., Sperling H., Börner M. and Beneke M. (2011). **Time to onset of action of vardenafil: a retrospective analysis of the pivotal trials for the orodispersible and film-coated tablet formulations**. *The Journal of Sexual Medicine*, *8*(10), 2912–2923. https://doi.org/10.1111/j.1743-6109.2011.02462.x

83. Dewitte M., Bettocchi C., Carvalho J., Corona G., Flink I., Limoncin E., Pascoal P., Reisman Y. and Van Lankveld J. (2021). **A Psychosocial Approach to Erectile Dysfunction: Position Statements from the European Society of Sexual Medicine (ESSM)**. *Sexual Medicine*, *9*(6), 100434. https://doi.org/10.1016/j.esxm.2021.100434

84. d'Emmanuele di Villa Bianca R., Sorrentino R., Sorrentino R., Imbimbo C., Palmieri A., Fusco F., Maggi M., De Palma R., Cirino G. and Mirone V. (2006). **Sphingosine 1-phosphate induces endothelial nitric-oxide synthase activation through phosphorylation in human corpus cavernosum**. *The Journal of Pharmacology and Experimental Therapeutics*, *316*(2), 703–708. https://doi.org/10.1124/jpet.105.093419

85. Dinsmore W.W. and Wyllie M.G. (2008). **Vasoactive intestinal polypeptide/phentolamine for intracavernosal injection in erectile dysfunction**. *BJU International*, *102*(8), 933–937. https://doi.org/10.1111/j.1464-410X.2008.07764.x

86. Donovan J. L., Hamdy F. C., Lane J.A., Mason M., Metcalfe C., Walsh E., Blazeby J.M., Peters T.J., Holding P., Bonnington S., Lennon T., Bradshaw L., Cooper D., Herbert P., Howson J., Jones A., Lyons N., Salter E., Thompson P., Neal D.E. (2016). **Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer**. *The New England Journal of Medicine*, *375*(15), 1425–1437. https://doi.org/10.1056/NEJMoa1606221

87. Dropkin B.M. and Kaufman M.R. (2021). **Antibiotics and Inflatable Penile Prosthesis Insertion: A Literature Review.** *Sexual Medicine Reviews*, *9*(1), 174–180. https://doi.org/10.1016/j.sxmr.2020.04.005

88. Duncan C., Omran G.J., Teh J., Davis N.F., Bolton D.M. and Lawrentschuk N. (2019). **Erectile dysfunction: a global review of intracavernosal injectables**. *World Journal of Urology*, *37*(6), 1007–1014. https://doi.org/10.1007/s00345-019-02727-5

89. Eardley I., Donatucci C., Corbin J., El-Melieg A., Hatzimouratidis K., McVary K., Munarriz R. and Lee S.W. (2010). **Pharmacotherapy for erectile dysfunction**. *The Journal of Sexual Medicine*, *7*(1 Pt 2), 524–540. https://doi.org/10.1111/j.1743-6109.2009.01627.x

90. Eardley I. (2013). **The Incidence, Prevalence and Natural History of Erectile Dysfunction**. *Sexual Medicine Reviews*, *1*(1), 3–16. https://doi.org/10.1002/smrj.2

91. Emanu J.C., Avildsen I.K. and Nelson C.J. (2016). **Erectile dysfunction after radical prostatectomy: prevalence, medical treatments, and psychosocial interventions**. *Current Opinion in Supportive and Palliative Care*, *10*(1), 10210. https://doi.org/10.1097/SPC.0000000000000195

92. Epifanova M., Kaprin A., Kostin A., Gvasalia B., Chalyy M., Artemenko S. and Epifanov A. (2020). **P-02-16 Combined Platelet-Rich Plasma and Shockwave Therapy in Erectile Dysfunction Treatment**. *The Journal of Sexual Medicine*, *17*(6), 176. https://doi.org/10.1016/j.jsxm.2020.04.170

93. Epifanova M.V., Gvasalia B.R., Durashov M.A. and Artemenko S.A. (2020). **Platelet-Rich Plasma Therapy for Male Sexual Dysfunction: Myth or Reality?** *Sexual Medicine Reviews*, *8*(1), 106–113. https://doi.org/10.1016/j.sxmr.2019.02.002

94. Falcone M., Rolle L., Ceruti C., Timpano M., Sedigh O., Preto M., Gonella A. and Frea B. (2013). **Prospective analysis of the surgical outcomes and patients' satisfaction rate after the AMS Spectra penile prosthesis implanttation**. *Urology*, *82*(2), 373–376. https://doi.org/10.1016/j.urology.2013.04.027

95. Fallara G., Capogrosso P., Maggio P., Taborelli A., Montorsi F., Dehò F. and Salonia A. (2021). **Erectile function after focal therapy for localized prostate cancer: a systematic review**. *International Journal of Impotence Research*, *33*(4), 418–427. https://doi.org/10.1038/s41443-020-00357-9

96. Feldman H.A., Goldstein I., Hatzichristou D.G., Krane R.J. and McKinlay J.B. (1994). **Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study**. *The Journal of Urology*, *151*(1), 54–61. https://doi.org/10.1016/s0022-5347(17)34871-1

97. Fenton J.J., Weyrich M.S., Durbin S., Liu Y., Bang H. and Melnikow J. (2018). **Prostate-Specific Antigen-Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force**. *JAMA*, *319*(18), 1914–1931. https://doi.org/10.1001/jama.2018.3712

98. Ferrini M.G., Kovanecz I., Sanchez S., Vernet D., Davila H.H., Rajfer J. and Gonzalez-Cadavid N.F. (2007). **Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat**. *Biology of Reproduction*, *76*(5), 915–923. https://doi.org/10.1095/biolreprod.106.059642

99. Ferrini M.G, Davila H.H., Kovanecz I., Sanchez S.P., Gonzalez-Cadavid N.F., and Rajfer J. (2006). **Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat**. *Urology*, *68*(2), 429–435. https://doi.org/10.1016/j.urology.2006.05.011

100. Ferrini M.G, Kovanecz I., Nolazco G., Rajfer J. and Gonzalez-Cadavid N.F. (2006). **Effects of long-term vardenafil treatment on the development of fibrotic plaques in a rat model of Peyronie's disease**. *BJU International*, *97*(3), 625–633. https://doi.org/10.1111/j.1464-410X.2006.05955.x

101. Ferrini M.G, Kovanecz I., Sanchez S., Umeh C., Rajfer J. and Gonzalez-Cadavid N.F. (2009). **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**. *The Journal of Sexual Medicine*, *6*(2), 415–428. https://doi.org/10.1111/j.1743-6109.2008.01105.x

102. Filippi S., Vignozzi L., Morelli A., Chavalmane A.K., Sarchielli E., Fibbi B., Saad F., Sandner P., Ruggiano P., Vannelli G.B., Mannucci E. and Maggi M. (2009). **Testosterone partially ameliorates metabolic profile and erectile responsiveness to PDE5 inhibitors in an animal model of male metabolic syndrome**. *The Journal of Sexual Medicine*, *6*(12), 3274–3288. https://doi.org/10.1111/j.1743-6109.2009.01467.x

103. Finkle W.D., Greenland S., Ridgeway G.K., Adams J.L., Frasco M.A., Cook M.B., Fraumeni J.F.J. and Hoover R.N. (2014). **Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men**. *PloS One*, *9*(1), e85805. https://doi.org/10.1371/journal.pone.0085805

104. Fode M., Hatzichristodoulou G., Serefoglu E. C., Verze P. and Albersen M. (2017). **Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough?** *Nature Reviews. Urology*, *14*(10), 593–606. https://doi.org/10.1038/nrurol.2017.119

105. Fojecki G.L., Tiessen S. and Osther P.J.S. (2017). **Effect of Low-Energy Linear Shockwave Therapy on Erectile Dysfunction-A Double-Blinded, Sham-Controlled, Randomized Clinical Trial**. *The Journal of Sexual Medicine*, *14*(1), 106–112. https://doi.org/10.1016/j.jsxm.2016.11.307

106. Forgue S.T., Patterson B.E., Bedding A.W., Payne C.D., Phillips D.L., Wrishko R.E. and Mitchell M.I. (2006). **Tadalafil pharmacokinetics in healthy subjects**. *British Journal of Clinical Pharmacology*, *61*(3), 280–288. https://doi.org/10.1111/j.1365-2125.2005.02553.x

107. Francis M.E., Kusek J.W., Nyberg L.M. and Eggers P.W. (2007). **The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males**. *The Journal of Urology*, *178*(2), 591–596; discussion 596. https://doi.org/10.1016/j.juro.2007.03.127

108. Frühauf S., Gerger H., Schmidt H.M., Munder T. and Barth, J. (2013). **Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis**. *Archives of Sexual Behavior*, *42*(6), 915–933. https://doi.org/10.1007/s10508-012-0062-0

109. Gabbay I.E. and Lavie P. (2012). **Age- and gender-related characteristics of obstructive sleep apnea**. *Sleep and Breathing = Schlaf and Atmung*, *16*(2), 453–460. https://doi.org/10.1007/s11325-011-0523-z

110. Gacci M., Andersson K.E., Chapple C., Maggi M., Mirone V., Oelke M., Porst H., Roehrborn C., Stief C. and Giuliano F. (2016). **Latest Evidence on the Use of Phosphodiesterase Type 5 Inhibitors for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia**. *European Urology*, *70*(1), 124–133. https://doi.org/10.1016/j.eururo.2015.12.048

111. Gaither T.W., Awad M.A., Osterberg E.C., Murphy G.P., Allen I. E., Chang A., Rosen R.C. and Breyer B.N. (2017). **The Natural History of Erectile Dysfunction After Prostatic Radiotherapy: A Systematic Review and Meta-Analysis**. *The Journal of Sexual Medicine*, *14*(9), 1071–1078. https://doi.org/10.1016/j.jsxm.2017.07.010

112. Garrido-Abad P., Senra-Bravo I., Manfredi C., Fernández-Pascual E., Linares-Espinós E., Fernández-Arjona M., Varillas-Delgado D. and Martínez-Salamanca J.I. (2022). **Combination therapy with topical alprostadil and phosphodiesterase-5 inhibitors after failure of oral therapy in patients with erectile dysfunction: a prospective, two-arm, open-label, non-randomized study**. *International Journal of Impotence Research*, *34*(2), 164–171. https://doi.org/10.1038/s41443-020-00400-9

113. Giannetta E., Gianfrilli D., Barbagallo F., Isidori A.M. and Lenzi A. (2012). **Subclinical male hypogonadism**. *Best Practice and Research. Clinical Endocrinology and Metabolism*, *26*(4), 539–550. https://doi.org/10.1016/j.beem.2011.12.005

114. Giltay E.J., Tishova Y.A., Mskhalaya G.J., Gooren L. J.G., Saad F. and Kalinchenko S.Y. (2010). **Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metablic syndrome**. *The Journal of Sexual Medicine*, *7*(7), 2572–2582. https://doi.org/10.1111/j.1743-6109.2010.01859.x

115. Giuliano F., Rampin O., Schirar A., Jardin A. and Rousseau J. P. (1993). **Autonomic control of penile erection: modulation by testosterone in the rat**. *Journal of Neuroendocrinology*, *5*(6), 677–683. https://doi.org/10.1111/j.1365-2826.1993.tb00539.x

116. Glickman L., Godoy G. and Lepor H. (2009). **Changes in continence and erectile function between 2 and 4 years after radical prostatectomy**. *The Journal of Urology*, *181*(2), 731–735. https://doi.org/10.1016/j.juro.2008.10.019

117. Glina S., Shindel A., Eardley I., Ghanem H. (2008). **Cavernosal α-blockade: a new technique for investigating and treating erectile impotence by GS Brindley**. *The Journal of Sexual Medicine*; 5:1791–1794. https://doi:10.1111/j.1743-6109.2008.00954.x

118. Goldberger J.J., Cain M.E., Hohnloser S.H., Kadish A.H., Knight B.P., Lauer M.S., Maron B.J., Page R.L., Passman R.S., Siscovick D., Stevenson W.G., and Zipes D.P. (2008). **American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A scientific statement from the Americ**. *Journal of the American College of Cardiology*, *52*(14), 1179–1199. https://doi.org/10.1016/j.jacc.2008.05.003

119. Gray P.B., Singh A.B., Woodhouse L., Storer T.W., Casaburi R., Dzekov J., Dzekov C., Sinha-Hiki I. and Bhasin S. (2005). **Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men**. *The Journal of Clinical Endocrinology and Metabolism*, *90*(7), 3838–3846. https://doi.org/10.1210/jc.2005-0247

120. Gregório M.G., Jacomelli M., Inoue D., Genta P.R., de Figueiredo A.C. and Lorenzi-Filho G. (2011). **Comparison of full versus short induced-sleep polysomnography for the diagnosis of sleep apnea**. *The Laryngoscope*, *121*(5), 1098–1103. https://doi.org/10.1002/lary.21658

121. Grimm R.H.J., Grandits G.A., Prineas R.J., McDonald R.H., Lewis C.E., Flack J.M., Yunis C., Svendsen K., Liebson P.R. and Elmer P.J. (1997). **Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS)**. *Hypertension*, *29*, 8–14. https://doi.org/10.1161/01.hyp.29.1.8

122. Gross M.S., Phillips E.A., Balen A., Eid J.F., Yang C., Simon R., Martinez D., Carrion R., Perito P., Levine L., Greenfield J. and Munarriz R. (2016). **The Malleable Implant Salvage Technique: Infection Outcomes after Mulcahy Salvage Procedure and Replacement of Infected Inflatable Penile Prosthesis with Malleable Prosthesis**. *The Journal of Urology*, *195*(3), 694–697. https://doi.org/10.1016/j.juro.2015.08.091

123. Gruenwald I., Appel B., Kitrey N.D. and Vardi Y. (2013). **Shockwave treatment of erectile dysfunction**. *Therapeutic Advances in Urology*, *5*(2), 95–99. https://doi.org/10.1177/1756287212470696

124. Gruenwald I., Appel B. and Vardi Y. (2012). **Low-intensity extracorporeal shock wave therapy--a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy**. *The Journal of Sexual Medicine*, *9*(1), 259–264. https://doi.org/10.1111/j.1743-6109.2011.02498.x

125. Gruenwald I., Shenfeld O., Chen J., Raviv G., Richter S., Cohen A. and Vardi Y. (2006). **Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil**. *European Urology*, *50*(1), 134–140. https://doi.org/10.1016/j.eururo.2006.01.042

126. Gupta R., Kirschen J., Barrow R.C. and EID J.F. (1997). **Predictors of Success and Risk Factors for Attrition in the Use of Intracavernous Injection**. *The Journal of Urology*, *157*(5), 1681–1686.

127. Gupta B.P., Murad M.H., Clifton M.M., Prokop L., Nehra A. and Kopecky S.L. (2011). **The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis**. *Archives of Internal Medicine*, *171*(20), 1797–1803. https://doi.org/10.1001/archinternmed.2011.440

128. Gur S., Kadowitz P.J., Gokce A., Sikka S.C., Lokman U. and Hellstrom W.J.G. (2013). **Update on drug interactions with phosphodiesterase-5 inhibitors prescribed as first-line therapy for patients with erectile dysfunction or pulmonary hypertension**. *Current Drug Metabolism*, *14*(2), 265–269. https://doi.org/10.2174/1389200211314020014

129. Habous M., Farag M., Williamson B., Laban O., Mahmoud S., Abdelwahab O., Elkhouly M., Kamil U., Binsaleh S., Tal R., Ralph D. and Mulhall, J.P. (2016). **Conservative Therapy is an Effective Option in Patients With Localized Infection After Penile Implant Surgery**. *The Journal of Sexual Medicine*, *13*(6), 972–976. https://doi.org/10.1016/j.jsxm.2016.04.064

130. Hackett G., Cole N., Bhartia M., Kennedy D., Raju J. and Wilkinson P. (2013). **Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes**. *The Journal of Sexual Medicine*, *10*(6), 1612–1627. https://doi.org/10.1111/jsm.12146

131. Haglind E., Carlsson S., Stranne J., Wallerstedt A., Wilderäng U., Thorsteinsdottir T., Lagerkvist M., Damber J.E., Bjartell A., Hugosson J., Wiklund P. and Steineck, G. (2015). **Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial**. *European Urology*, *68*(2), 216–225. https://doi.org/10.1016/j.eururo.2015.02.029

132. Hatzichristou D., Moysidis K., Apostolidis A., Bekos A., Tzortzis V., Hatzimouratidis K. and Ioannidis E. (2005). **Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100 non-responders**. *European Urology*, *47*(4), 513–518. https://doi.org/10.1016/j.eururo.2004.12.005

133. Hatzichristou D., Rosen R.C., Derogatis L.R., Low W.Y., Meuleman E.J.H., Sadovsky R. and Symonds T. (2010**). Recommendations for the clinical evaluation of men and women with sexual dysfunction**. *The Journal of Sexual Medicine*, *7*(1 Pt 2), 337–348. https://doi.org/10.1111/j.1743-6109.2009.01619.x

134. Hatzimouratidis K., Eardley I., Giuliano F., Hatzichristou D., Moncada I., Salonia A., Vardi Y. and Wespes, E. (2012). **EAU guidelines on penile curvature**. *European Urology*, *62*(3), 543–552. https://doi.org/10.1016/j.eururo.2012.05.040

135. Hatzimouratidis K., Salonia A., Adaikan G., Buvat J., Carrier S., El-Meliegy A., McCullough A., Torres L.O. and Khera M. (2016). **Pharmacotherapy for Erectile Dysfunction: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015)**. *The Journal of Sexual Medicine*, *13*(4), 465–488. https://doi.org/10.1016/j.jsxm.2016.01.016

136. Hellstrom W.J.G., Montague D.K., Moncada I., Carson C., Minhas S., Faria G. and Krishnamurti, S. (2010). **Implants, mechanical devices, and vascular surgery for erectile dysfunction**. *The Journal of Sexual Medicine*, *7*(1 Pt 2), 501–523. https://doi.org/10.1111/j.1743-6109.2009.01626.x

137. Henry G.D., Brinkman M.J., Mead S.F., Delk J.R. 2nd, Cleves M.A., Jennermann C., Wilson S.K. and Kramer A.C. (2012). **A survey of patients with inflatable penile prostheses: assessment of timing and frequency of intercourse and analysis of implant durability**. *The Journal of Sexual Medicine*, *9*(6), 1715–1721. https://doi.org/10.1111/j.1743-6109.2012.02729.x

138. Henry G.D., Donatucci C.F., Conners W., Greenfield J.M., Carson C.C., Wilson S.K., Delk J., Lentz A.C., Cleves M.A., Jennermann C.J. and Kramer A.C. (2012). **An outcomes analysis of over 200 revision surgeries for penile prosthesis implantation: a multicenter study**. *The Journal of Sexual Medicine*, *9*(1), 309–315. https://doi.org/10.1111/j.1743-6109.2011.02524.x

139. Hisasue S., China T., Horiuchi A., Kimura M., Saito K., Isotani S., Ide H., Muto S., Yamaguchi R. and Horie S. (2016). **Impact of aging and comorbiddity on the efficacy of low-intensity shock wave therapy for erectile dysfunction**. *International Journal of Urology : Official Journal of the Japanese Urological Association*, *23*(1), 80–84. https://doi.org/10.1111/iju.12955

140. Hoyos C.M., Melehan K.L., Phillips C.L., Grunstein R.R. and Liu P.Y. (2015). **To ED or not to ED--is erectile dysfunction in obstructive sleep apnea related to endothelial dysfunction?** *Sleep Medicine Reviews*, *20*, 5–14. https://doi.org/10.1016/j.smrv.2014.03.004

141. Hsu W.Y., Chiu N.Y., Chang C.C., Chang, T.G. and Lane H.Y. (2019). **The association between cigarette smoking and obstructive sleep apnea**. *Tobacco Induced Diseases*, *17*, 27. https://doi.org/10.18332/tid/105893

142. Hull E.M., Lorrain D.S., Du J., Matuszewich L., Lumley L.A., Putnam S.K., and Moses J. (1999). **Hormone-neurotransmitter interactions in the control of sexual behavior**. *Behavioural Brain Research*, *105*(1), 105–116. https://doi.org/10.1016/s0166-4328(99)00086-8

143. Hunt A.A., Choudhury K.R., Nukala V., Nolan M.W., Ahmad A., Ashcraft K.A. and Koontz B.F. (2021). **Risk of erectile dysfunction after modern radiotherapy for intact prostate cancer**. *Prostate Cancer and Prostatic Diseases*, *24*(1), 128–134. https://doi.org/10.1038/s41391-020-0247-x

144. Hunter S.S., Gadallah A., Azawi M.K. and Doss W. (2014). **Erectile dysfunction in patients with chronic hepatitis C virus infection**. *Arab Journal of Gastroenterology : The Official Publication of the Pan-Arab Association of Gastroenterology*, *15*(1), 16–20. https://doi.org/10.1016/j.ajg.2014.01.012

145. Iovino P., Pascariello A., Limongelli P. et al. (2007). **The prevalence of sexual behavior disorders in patients with treated and untreated gastroesophageal reflux disease**. Surg. Endosc.;21(7):1104-1110. https://doi:10.1007/s00464-007-9264-2

146. İrer B., Çelikhisar A., Çelikhisar H., Bozkurt O. and Demir, Ö. (2018). **Evaluation of Sexual Dysfunction, Lower Urinary Tract Symptoms and Quality of Life in Men With Obstructive Sleep Apnea Syndrome and the Efficacy of Continuous Positive Airway Pressure Therapy**. *Urology*, *121*, 86–92. https://doi.org/10.1016/j.urology.2018.08.001

147. Isgoren A.E., Saitz T.R. and Serefoglu E.C. (2014). **Erectile Function Outcomes after Robot-Assisted Radical Prostatectomy: Is It Superior to Open Retropubic or Laparoscopic Approach?** *Sexual Medicine Reviews*, *2*(1), 1023. https://doi.org/10.1002/smrj.21

148. Isidori A.M., Balercia G., Calogero A.E., Corona G., Ferlin A., Francavilla S., Santi D. and Maggi M. (2015). **Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology**. *Journal of Endocrinological Investigation*, *38*(1), 103–112. https://doi.org/10.1007/s40618-014-0155-9

149. Isidori A.M., Buvat J., Corona G., Goldstein I., Jannini E.A., Lenzi A., Porst H., Salonia A., Traish A.M. and Maggi, M. (2014). **A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review**. *European Urology*, *65*(1), 99–112. https://doi.org/10.1016/j.eururo.2013.08.048

150. Jehan S., Zizi F., Pandi-Perumal S.R., Wall S., Auguste E., Myers A.K., Jean-Louis G. and McFarlane S.I. (2017). **Obstructive Sleep Apnea and Obesity: Implications for Public Health**. *Sleep Medicine and Disorders: International Journal*, *1*(4). https://doi.org/10.15406/smdij.2017.01.00019

151. Ju I. E., Trieu D., Chang S.B., Mungovan S.F. and Patel M.I. (2021). **Surgeon Experience and Erectile Function After Radical Prostatectomy: A Systematic Review**. *Sexual Medicine Reviews*, *9*(4), 650–658. https://doi.org/10.1016/j.sxmr.2020.09.006

152. Kalejaiye O., Raheem A.A., Moubasher A., Capece M., McNeillis S., Muneer A., Christopher A.N., Garaffa G. and Ralph D.J. (2017**). Sleep disorders in patients with erectile dysfunction**. *BJU International*, *120*(6), 855–860. https://doi.org/10.1111/bju.13961

153. Kalyvianakis D. and Hatzichristou D. (2017**). Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial**. *The Journal of Sexual Medicine*, *14*(7), 891–897. https://doi.org/10.1016/j.jsxm.2017.05.012

154. Kellesarian S.V, Malignaggi V.R., Feng C. and Javed F. (2018). **Association between obstructive sleep apnea and erectile dysfunction: a systematic review and meta-analysis**. *International Journal of Impotence Research*, *30*(3), 129–140. https://doi.org/10.1038/s41443-018-0017-7

155. Kessler A., Sollie S., Challacombe B., Briggs K. and Van Hemelrijck M. (2019). **The global prevalence of erectile dysfunction: a review**. *BJU International*. https://doi.org/10.1111/bju.14813

156. Kezirian E.J., Hohenhorst W. and de Vries N. (2011). **Drug-induced sleep endoscopy: the VOTE classification**. *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, *268*(8), 1233–1236. https://doi.org/10.1007/s00405-011-1633-8

157. Khaire S.S., Gada J.V, Utpat K.V, Shah N., Varthakavi P.K. and Bhagwat N.M. (2020). **A study of glycemic variability in patients with type 2 diabetes mellitus with obstructive sleep apnea syndrome using a continuous glucose monitoring system**. *Clinical Diabetes and Endocrinology*, *6*, 10. https://doi.org/10.1186/s40842-020-00098-0

158. Khoder W.Y., Waidelich R., Seitz M., Becker A.J., Buchner A., Trittschler S. and Stief C.G. (2015). **Do we need the nerve sparing radical prostatectomy techniques (intrafascial vs. interfascial) in men with erectile dysfunction? Results of a single-centre study**. *World Journal of Urology*, *33*(3), 301–307. https://doi.org/10.1007/s00345-014-1302-9

159. Kim J.H., Lee H.J. and Song Y.S. (2016). **Mesenchymal stem cell-based gene therapy for erectile dysfunction**. *International Journal of Impotence Research*, *28*(3), 81–87. https://doi.org/10.1038/ijir.2016.3

160. Kim M., Kim S.Y., Rou W.S., Hwang S.W. and Lee B.S. (2015). **Erectile dysfunction in patients with liver disease related to chronic hepatitis B**. *Clinical and Molecular Hepatology*, *21*(4), 352–357. https://doi.org/10.3350/cmh.2015.21.4.352

161. Kitrey N.D., Gruenwald I., Appel B., Shechter A., Massarwa O. and Vardi Y. (2016). **Penile Low Intensity Shock Wave Treatment is Able to Shift PDE5i Nonresponders to Responders: A Double-Blind, Sham Controlled Study**. *The Journal of Urology*, *195*(5), 1550–1555. https://doi.org/10.1016/j.juro.2015.12.049

162. Kloner R.A. (2004). **Novel phosphodiesterase type 5 inhibitors: assessing hemodynamic effects and safety parameters**. *Clinical Cardiology*, *27*(4 Suppl 1), I20-5. https://doi.org/10.1002/clc.4960271306

163. **Kloner R.A., Goldstein I., Kirby M.G., Parker J.D. and Sadovsky R. (2018). Cardiovascular Safety of Phosphodiesterase Type 5 Inhibitors After Nearly 2 Decades on the Market.** *Sexual Medicine Reviews*, *6*(4), 583–594. https://doi.org/10.1016/j.sxmr.2018.03.008

164. Kovanecz I., Rambhatla A., Ferrini M.G., Vernet D., Sanchez S., Rajfer J. and Gonzalez-Cadavid N. (2008). **Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection**. *BJU International*, *101*(2), 203–210. https://doi.org/10.1111/j.1464-410X.2007.07223.x

165. Kupelian V., Araujo A.B., Chiu G.R., Rosen R.C. and McKinlay J.B. (2010). **Relative contributions of modifiable risk factors to erectile dysfunction: results from the Boston Area Community Health (BACH) Survey**. *Preventive Medicine*, *50*(1–2), 19–25. https://doi.org/10.1016/j.ypmed.2009.11.006

166. Kumsar N.A., Kumsar S., Dilbaz N. (2016). **Sexual dysfunction in men diagnosed as substance use disorder**. *Andrologia*; 48(10):1229- 1235. https://doi:10.1111/and.12566

167. Kwan M., Greenleaf W.J., Mann J., Crapo L. and Davidson J.M. (1983). **The nature of androgen action on male sexuality: a combined laboratory-self-report study on hypogonadal men**. *The Journal of Clinical Endocrinology and Metabolism*, *57*(3), 557–562. https://doi.org/10.1210/jcem-57-3-557

168. Kyle J.A., Brown D.A. and Hill, J.K. (2013). **Avanafil for erectile dysfunction**. *The Annals of Pharmacotherapy*, *47*(10), 1312–1320. https://doi.org/10.1177/1060028013501989

169. Lacchini R., Muniz J.J., Nobre Y.T.D.A., Cologna A.J., Martins A.C.P. and Tanus-Santos J.E. (2018). **Influence of arginase polymorphisms and arginase levels/activity on the response to erectile dysfunction therapy with sildenafil**. *The Pharmacogenomics Journal*, *18*(2), 238–244. https://doi.org/10.1038/tpj.2017.2

170. Ladegaard P.B.J., Mortensen J., Skov-Jeppesen S.M. and Lund L. (2021). **Erectile Dysfunction A Prospective Randomized Placebo-Controlled Study Evaluating the Effect of Low-Intensity Extracorporeal Shockwave Therapy (LI-ESWT) in Men With Erectile Dysfunction Following Radical Prostatectomy**. *Sexual Medicine*, *9*(3), 100338. https://doi.org/10.1016/j.esxm.2021.100338

171. Lakin M.M., Montague D.K., VanderBrug Medendorp S., Tesar L. and Schover L.R. (1990). **Intracavernous injection therapy: analysis of results and complications**. *The Journal of Urology*, *143*(6), 1138–1141. https://doi.org/10.1016/s0022-5347(17)40208-4

172. Laratta C.R., Ayas N.T., Povitz M. and Pendharkar S.R. (2017). **Diagnosis and treatment of obstructive sleep apnea in adults**. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *189*(48), E1481–E1488. https://doi.org/10.1503/cmaj.170296

173. Lardas M., Liew M., van den Bergh R.C., De Santis M., Bellmunt J., Van den Broeck T., Cornford P., Cumberbatch M.G., Fossati N., Gross T., Henry A.M., Bolla M., Briers E., Joniau S., Lam T.B., Mason M.D., Mottet N., van der Poel H.G., Rouvière O., Bourke L. (2017**). Quality of Life Outcomes after Primary Treatment for Clinically Localised Prostate Cancer: A Systematic Review**. *European Urology*, *72*(6), 869–885. https://doi.org/10.1016/j.eururo.2017.06.035

174. Lee D., Romero C., Alba F., Westney O.L. and Wang R. (2013). **Simultaneous penile prosthesis and male sling/artificial urinary sphincter**. *Asian Journal of Andrology*, *15*(1), 10–15. https://doi.org/10.1038/aja.2012.115

175. Lee D., Westney O.L. and Wang R. (2011). **Combination surgery for erectile dysfunction and male incontinence**. *Current Urology Reports*, *12*(6), 461–469. https://doi.org/10.1007/s11934-011-0220-2

176. Leungwattanakij S., Bivalacqua T.J., Usta M.F., Yang D.Y., Hyun J.S., Champion H.C., Abdel-Mageed A.B. and Hellstrom W.J.G. (2003). **Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum**. *Journal of Andrology*, *24*(2), 239–245. https://doi.org/10.1002/j.1939-4640.2003.tb02668.x

177. Levine LA and Dimitriou R.J. (2001). **Vacuum constriction and external erection devices in erectile dysfunction**. *The Urologic Clinics of North America*, *28*(2), 335–341, ix–x. https://doi.org/10.1016/s0094-0143(05)70142-7

178. Levine Laurence A., Becher E.F., Bella A.J., Brant W.O., Kohler T.S., Martinez-Salamanca J.I., Trost L. and Morey A.F. (2016). **Penile Prosthesis Surgery: Current Recommendations From the International Consultation on Sexual Medicine**. *The Journal of Sexual Medicine*, *13*(4), 489–518. https://doi.org/10.1016/j.jsxm.2016.01.017

179. Levine Laurence A. and Burnett A.L. (2013). **Standard operating procedures for Peyronie's disease**. *The Journal of Sexual Medicine*, *10*(1), 230–244. https://doi.org/10.1111/j.1743-6109.2012.03003.x

180. Lewis R.W. and Witherington R. (1997). **External vacuum therapy for erectile dysfunction: use and results**. *World Journal of Urology*, *15*(1), 78–82. https://doi.org/10.1007/BF01275162

181. Li X., Dong Z., Wan Y. and Wang Z. (2010). **Sildenafil versus continuous positive airway pressure for erectile dysfunction in men with obstructive sleep apnea: a meta-analysis**. *The Aging Male: The Official Journal of the International Society for the Study of the Aging Male*, *13*(2), 82–86. https://doi.org/10.3109/13685530903406789

182. Liao W., Huang W., Guo Y., Xin M. and Fu X. (2013). **Testosterone promotes vascular endothelial cell migration via upregulation of ROCK-2/moesin cascade**. *Molecular Biology Reports*, *40*(12), 6729–6735. https://doi.org/10.1007/s11033-013-2788-8

183. Lipsky M.J., Onyeji I., Golan R., Munarriz R., Kashanian J.A., Stember D.S. and Stahl P.J. (2019). **Diabetes Is a Risk Factor for Inflatable Penile Prosthesis Infection: Analysis of a Large Statewide Database**. *Sexual Medicine*, *7*(1), 35–40. https://doi.org/10.1016/j.esxm.2018.11.007

184. Loi M., Wortel R.C., Francolini G. and Incrocci L. (2019). **Sexual Function in Patients Treated With Stereotactic Radiotherapy For Prostate Cancer: A Systematic Review of the Current Evidence**. *The Journal of Sexual Medicine*, *16*(9), 1409–1420. https://doi.org/10.1016/j.jsxm.2019.05.019

185. Lokeshwar S.D., Patel P., Shah S.M. and Ramasamy R. (2020). **A Systematic Review of Human Trials Using Stem Cell Therapy for Erectile Dysfunction**. *Sexual Medicine Reviews*, *8*(1), 122–130. https://doi.org/10.1016/j.sxmr.2019.08.003

186. Lu Z., Lin G., Reed-Maldonado A., Wang C., Lee Y.C. and Lue T.F. (2017). **Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis**. *European Urology*, *71*(2), 223–233. https://doi.org/10.1016/j.eururo.2016.05.050

187. Lue T.F. (2000). **Erectile dysfunction**. *The New England Journal of Medicine*, *342*(24), 1802–1813. https://doi.org/10.1056/NEJM200006153422407

188. Lue T.F. and Tanagho E.A. (1987). **Physiology of erection and pharmacological management of impotence**. *The Journal of Urology*, *137*(5), 829–836. https://doi.org/10.1016/s0022-5347(17)44267-4

189. Lugg J., Ng C., Rajfer J. and González-Cadavid N. (1996**). Cavernosal nerve stimulation in the rat reverses castration-induced decrease in penile NOS activity**. *The American Journal of Physiology*, *271*(2 Pt 1), E354-61. https://doi.org/10.1152/ajpendo.1996.271.2.E354

190. Lux M., Reyes-Vallejo L., Morgentaler A. and Levine L.A. (2007). **Outcomes and satisfaction rates for the redesigned 2-piece penile prosthesis**. *The Journal of Urology*, *177*(1), 262–266. https://doi.org/10.1016/j.juro.2006.08.094

191. Madeira C.R., Tonin F.S., Fachi M.M., Borba H.H., Ferreira V.L., Leonart L.P., Bonetti A.F., Moritz R.P., Trindade A.C.L.B., Gonçalve A.G., Fernandez-Llimos F. and Pontarolo R. (2021). **Efficacy and safety of oral phosphodiesterase 5 inhibitors for erectile dysfunction: a network meta-analysis and multicriteria decision analysis**. *World Journal of Urology*, *39*(3), 953–962. https://doi.org/10.1007/s00345-020-03233-9

192. Maggi M., Buvat J., Corona G., Guay A. and Torres L. O. (2013). **Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA)**. *The Journal of Sexual Medicine*, *10*(3), 661–677. https://doi.org/10.1111/j.1743-6109.2012.02735.x

193. Maggi M., Gentilucci A., Salciccia S., Gatto A., Gentile V., Colarieti A., Von Heland M., Busetto G.M., Del Giudice F. and Sciarra A. (2019). **Psychological impact of different primary treatments forprostate cancer: A critical analysis**. *Andrologia*, *51*(1), e13157. https://doi.org/10.1111/and.13157

194. Mahon J., Dornbier R., Wegrzyn G., Faraday M.M., Sadeghi-Nejad H., Hakim L. and McVary K.T. (2020). **Infectious Adverse Events Following the Placement of a Penile Prosthesis: A Systematic Review**. *Sexual Medicine Reviews*, *8*(2), 348–354. https://doi.org/10.1016/j.sxmr.2019.07.005

195. Mandava S.H., Serefoglu E.C., Freier M.T., Wilson S.K. and Hellstrom W.J.G. (2012). **Infection retardant coated inflatable penile prostheses decrease the incidence of infection: a systematic review and meta-analysis**. *The Journal of Urology*, *188*(5), 1855–1860. https://doi.org/10.1016/j.juro.2012.07.022

196. Manfredi C., Arcaniolo D., Spatafora P., Crocerossa F., Fusco F., Verze P., Fiori C., Damiano R., Cindolo L., De Sio M., Otero J. (2022). **Emerging minimally invasive transurethral treatments for benign prostatic hyperplasia: a systematic review with meta-analysis of functional outcomes and description of complications**. *Minerva Urology and Nephrology*, 74(4), 388-389. https://doi.org/10.23736/S2724-6051.21.04530-4

197. Marchal-Escalona C., Herrera-Imbroda B., Clemente-Postigo M., Alcaide-Torres J., Quiñonero A., Marchal M., Queipo-Ortuño M.I., Aragón I.M., Martín-Morales A., Lara M.F. and Cardona F. (2016). **PDE5A Polymorphisms Influence on Sildenafil Treatment Success**. *The Journal of Sexual Medicine*, *13*(7), 1104–1110. https://doi.org/10.1016/j.jsxm.2016.04.075

198. Matz E.L., Pearlman A.M. and Terlecki R.P. (2018). **Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions**. *Investigative and Clinical Urology*, *59*(1), 61–65. https://doi.org/10.4111/icu.2018.59.1.61

199. Matz E.L., Terlecki R., Zhang Y., Jackson J. and Atala A. (2019). **Stem Cell Therapy for Erectile Dysfunction**. *Sexual Medicine Reviews*, *7*(2), 321–328. https://doi.org/10.1016/j.sxmr.2017.12.008

200. Mazzucco L., Balbo V., Cattana E., Guaschino R. and Borzini P. (2009). **Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Plateltex and one manual procedure**. *Vox Sanguinis*, *97*(2), 110–118. https://doi.org/10.1111/j.1423-0410.2009.01188.x

201. McCab M.P. and Althof S.E. (2014). **A systematic review of the psychosocial outcomes associated with erectile dysfunction: does the impact of erectile dysfunction extend beyond a man's inability to have sex?** *The Journal of Sexual Medicine*, *11*(2), 347–363. https://doi.org/10.1111/jsm.12374

202. McCullough A.R., Barada J.H., Fawzy A., Guay A.T. and Hatzichristou D. (2002). **Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction**. *Urology*, *60*(2 Suppl 2), 28–38. https://doi.org/10.1016/s0090-4295(02)01688-6

203. McMahon C.G., Samali R. and Johnson H. (1999). **Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy**. *The Journal of Urology*, *162* (6), 1992–1998. https://doi.org/10.1016/s0022-5347(05)68085-8

204. McVary K.T., Carrier S. and Wessells H. (2001). **Smoking and erectile dysfunction: evidence based analysis**. *The Journal of Urology*, *166*(5), 16241632. https://doi.org/10.1016/S0022-5347(05)65641-8

205. Meinhardt W., Lycklama à Nijeholt A.A., Kropman R.F., Vermeij P. and Zwartendijk J. (1994). **Comparison of a mixture of papaverine, phentolamine and prostaglandin E1 with other intracavernous injections**. *European Urology*, *26*(4), 319–321. https://doi.org/10.1159/000475407

206. Mills T.M., Lewis R.W. and Stopper V.S. (1998). **Androgenic maintenance of inflow and veno-occlusion during erection in the rat**. *Biology of Reproduction*, *59*(6), 1413–1418. https://doi.org/10.1095/biolreprod59.6.1413

207. Modh R.A., Mulhall J.P. and Gilbert S.M. (2014). **Sexual dysfunction after cystectomy and urinary diversion**. *Nature Reviews. Urology*, *11*(8), 445–453. https://doi.org/10.1038/nrurol.2014.151

208. Moncada I., Jara J., Subirá D., Castaño I. and Hernández C. (2004). **Efficacy of sildenafil citrate at 12 hours after dosing: re-exploring the therapeutic window**. *European Urology*, *46*(3), 351–357. https://doi.org/10.1016/j.eururo.2004.04.025

209. Montague D.K. (2011). **Penile prosthesis implantation in the era of medical treatment for erectile dysfunction**. *The Urologic Clinics of North America*, *38*(2), 217–225. https://doi.org/10.1016/j.ucl.2011.02.009

210. Montorsi F., Adaikan G., Becher E., Giuliano F., Khoury S., Lue T.F., Sharlip I., Althof S.E., Andersson K.E., Brock G., Broderick G., Burnett A., Buvat J., Dean J., Donatucci C., Eardley I., Fugl-Meyer K.S., Goldstein I., Hackett G., Wasserman M. (2010). **Summary of the recommendations on sexual dysfunctions in men**. *The Journal of Sexual Medicine*, *7*(11), 3572–3588. https://doi.org/10.1111/j.1743-6109.2010.02062.x

211. Montorsi F., Nathan H.P., McCullough A., Brock G.B., Broderick G., Ahuja S., Whitaker S., Hoover A., Novack D., Murphy A. and Varanese L. (2004). **Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial**. *The Journal of Urology*, *172*(3), 1036–1041. https://doi.org/10.1097/01.ju.0000136448.71773.2b

212. Montorsi F., Oelke M., Henneges C., Brock G., Salonia A., d'Anzeo G., Rossi A., Mulhall J.P. and Büttner H. (2016). **Exploratory Decision-Tree Modeling of Data from the Randomized REACTT Trial of Tadalafil Versus Placebo to Predict Recovery of Erectile Function After Bilateral Nerve-Sparing Radical Prostatectomy**. *European Urology*, *70*(3), 529–537. https://doi.org/10.1016/j.eururo.2016.02.036

213. Montorsi F., Padma-Nathan H., Buvat J., Schwaibold H., Beneke M., Ulbrich E., Bandel T.J. and Porst H. (2004). **Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial**. *The Journal of Sexual Medicine*, *1*(2), 168–178. https://doi.org/10.1111/j.1743-6109.2004.04025.x

214. Moreland R.B. (1998). **Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence**. *International Journal of Impotence Research*, *10*(2), 113–120. https://doi.org/10.1038/sj.ijir.3900328

215. Moreland R.B., Traish A., McMillin M.A., Smith B., Goldstein I. and Saenz de Tejada I. (1995). **PGE1 suppresses the induction of collagen synthesis by transforming growth factor-beta 1 in human corpus cavernosum smooth muscle**. *The Journal of Urology*, *153*(3 Pt 1), 826–834. https://doi.org/10.1097/00005392-199503000-00082

216. Morelli A., Filippi S., Mancina R., Luconi M., Vignozzi L., Marini M., Orlando C., Vannelli G.B., Aversa A., Natali A., Forti G., Giorgi M., Jannini E.A., Ledda F. and Maggi M. (2004). **Androgens regulate phosphordiesterase type 5 expression and functional activity in corpora cavernosa**. *Endocrinology*, *145*(5), 2253–2263. https://doi.org/10.1210/en.2003-1699

217. Morgentaler A. (2014). **Testosterone, cardiovascular risk, and hormonophobia**. *The Journal of Sexual Medicine*, *11*(6), 1362–1366. https://doi.org/10.1111/jsm.12556

218. Moriel E.Z. and Rajfer J. (1993). **Sodium bicarbonate alleviates penile pain induced by intracavernous injections for erectile dysfunction**. *The Journal of Urology*, *149*(5 Pt 2), 1299–1300. https://doi.org/10.1016/s0022-5347(17)36373-5

219. Mostafa T., Hassan A., Alghobary M.F. and Abdelrahman S. H. (2020). **Effect of Genetic Polymorphism on the Response to PDE5 Inhibitors in Patients With Erectile Dysfunction: A Systematic Review and a Critical Appraisal**. *Sexual medicine reviews* 8(4), 573–585. https://doi.org/10.1016/j.sxmr.2020.05.005

220. Mottet N., Bellmunt J., Bolla M., Briers E., Cumberbatch M.G., De Santis M., Fossati N., Gross T., Henr A.M., Joniau S., Lam T.B., Mason M.D., Matveev V.B., Moldovan P.C., van den Bergh R.C.N., Van den Broeck T., van der Poel H.G., van der Kwast T.H., Rouvière O.,…...and Cornford P. (2017). **EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent**. *European Urology*, *71*(4), 618–629. https://doi.org/10.1016/j.eururo.2016.08.003

221. Moyad M.A., Barada J.H., Lue T.F., Mulhall J.P., Goldstein I. and Fawzy A. (2004). **Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part II**. *The Urologic Clinics of North America*, *31*(2), 259–273. https://doi.org/10.1016/j.ucl.2004.01.007

222. Mulcahy J.J. (2000). **Long-term experience with salvage of infected penile implants**. *The Journal of Urology*, *163*(2), 481–482. https://doi.org/10.1016/S0022-5347(05)67906-2

223. Mulcahy J.J, Austoni E., Barada J. H., Choi H.K., Hellstrom W.J., Krishnamurti S., Moncada I., Schultheiss D., Sohn M. and Wessells H. (2004). **The penile implant for erectile dysfunction**. *The Journal of Sexual Medicine*, *1*(1), 98–109. https://doi.org/10.1111/j.1743-6109.2004.10115.x

224. Mulhall J.P., Daller M., Traish A.M., Gupta S., Park K., Salimpour P., Payton T.R., Krane R.J. and Goldstein I. (1997). **Intracavernosal forskolin: role in management of vasculogenic impotence resistant to standard 3-agent pharmacotherapy**. *The Journal of Urology*, *158*(5), 1752–1759. https://doi.org/10.1016/s0022-5347(01)64118-1

225. Mulhall J.P., Jahoda A.E., Ahmed A. and Parker M. (2001). **Analysis of the consistency of intraurethral prostaglandin E (1) (MUSE) during at-home use**. *Urology*, *58*(2), 262–266. https://doi.org/10.1016/s0090-4295(01)01164-5

226. Mulhall J.P., Müller A., Donohue J.F., Mullerad M., Kobylarz K., Paduch D.A., Tal R., Li P.S., Cohen-Gould L. and Scardino P.T. (2008). **The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate**. *The Journal of Sexual Medicine*, *5*(5), 1126–1136. https://doi.org/10.1111/j.1743-6109.2008.00794.x

227. Muneer A., Fowler S., David J.R, Duncan J., Summerton R.W.R. (2020). **UK practice for penile prosthesis surgery: baseline analysis of the British Association of Urological Surgeons (BAUS) Penile Prosthesis Audit**. *BJU International*, *127*(3), 326–331. https://doi.org/10.1111/bju.15219

228. Nason G.J., McNamara F., Twyford M., O'Kelly F., White S., Dunne E., Durkan G.C., Giri S.K., Smyth G.P. and Power R.E. (2016). **Efficacy of vacuum erectile devices (VEDs) after radical prostatectomy: the initial Irish experience of a dedicated VED clinic**. *International Journal of Impotence Research*, *28*(6), 205–208. https://doi.org/10.1038/ijir.2016.23

229. Natali A., Olianas R. and Fisch M. (2008). **Penile implantation in Europe: successes and complications with 253 implants in Italy and Germany**. *The Journal of Sexual Medicine*, *5*(6), 1503–1512. https://doi.org/10.1111/j.1743-6109.2008.00819.x

230. Nehra A, Goldstein I., Pabby A., Nugent M., Huang Y.H., de las Morenas A., Krane R.J., Udelson D., Saenz de Tejada I. and Moreland R.B. (1996). **Mechanisms of venous leakage: a prospective clinicopathological correlation of corporeal function and structure**. *The Journal of Urology*, *156*(4), 1320–1329. https://doi.org/10.1016/s0022-5347(01)65578-2

231. Nehra A., Jackson G., Miner M., Billups K.L., Burnett A.L., Buvat J., Carson C.C., Cunningham G.R., Ganz P., Goldstein I., Guay A.T., Hackett G., Kloner R.A., Kostis J., Montorsi P., Ramsey M., Rosen R., Sadovsky R., Seftel A.D., Wu F.C.W. (2012). **The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease**. *Mayo Clinic Proceedings*, *87*(8), 766–778. https://doi.org/10.1016/j.mayocp.2012.06.015

232. Nichols D.J., Muirhead G.J. and Harness J.A. (2002). **Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality**. *British Journal of Clinical Pharmacology*, *53 Suppl.*, 5S-12S. https://doi.org/10.1046/j.0306-5251.2001.00027.x

233. Nolsøe A.B., Jensen C.F.S., Østergren P.B. and Fode M. (2021). **Neglected side effects to curative prostate cancer treatments**. *International Journal of Impotence Research*, *33*(4), 428–438. https://doi.org/10.1038/s41443-020-00386-4

234. Novara G., Ficarra V., Mocellin S., Ahlering T.E., Carroll P.R., Graefen M., Guazzoni G., Menon M., Patel V.R., Shariat S.F., Tewari A.K., Van Poppel H., Zattoni F., Montorsi F., Mottrie A., Rosen R.C. and Wilson T.G. (2012). **Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy**. *European Urology*, *62*(3), 382–404. https://doi.org/10.1016/j.eururo.2012.05.047

235. Ohmori T., Yatomi Y., Osada M., Kazama F., Takafuta T., Ikeda H. and Ozaki Y. (2003). **Sphingosine 1-phosphate induces contraction of coronary ar-tery smooth muscle cells via S1P2**. *Cardiovascular Research*, *58*(1), 170–177. https://doi.org/10.1016/s0008-6363(03)00260-8

236. Olsen A.B., Persiani M., Boie S., Hanna M. and Lund L. (2015). **Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study**. *Scandinavian Journal of Urology*, *49*(4), 329–333. https://doi.org/10.3109/21681805.2014.984326

237. Otero J.R., Cruz C.R., Gómez B.G., Geli J.S., Polo J.M., Castañé E.R. and Antolín A.R. (2017). **Comparison of the patient and partner satisfaction with 700CX and Titan penile prostheses**. *Asian Journal of Andrology*, *19*(3), 321–325. https://doi.org/10.4103/1008-682X.172822

238. Oudelaar B.W., Peerbooms J.C., Huis In 't Veld R. and Vochteloo A.J.H. (2019). **Concentrations of Blood Components in Commercial Platelet-Rich Plasma Separation Systems: A Review of the Literature**. *The American Journal of Sports Medicine*, *47*(2), 479–487. https://doi.org/10.1177/0363546517746112

239. Padma-Nathan H, Hellstrom W.J., Kaiser F.E., Labasky R.F., Lue T.F., Nolten W.E., Norwood P.C., Peterson C.A., Shabsigh R., Tam P.Y., Place V.A. and Gesundheit N. (1997). **Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group**. *The New England Journal of Medicine*, *336*(1), 1–7. https://doi.org/10.1056/NEJM199701023360101

240. Padma-Nathan H, Stecher V.J., Sweeney M., Orazem J., Tseng L.J. and Deriesthal H. (2003). **Minimal time to successful intercourse after sildenafil citrate: results of a randomized, double-blind, placebo-controlled trial**. *Urology*, *62*(3), 400–403. https://doi.org/10.1016/s0090-4295(03)00567-3

241. Padma-Nathan H. and Yeager J.L. (2006). **An integrated analysis of alprostadil topical cream for the treatment of erectile dysfunction in 1732 patients**. *Urology*, *68*(2), 386-391. https://doi.org/10.1016/j.urology.2006.02.027

242. Pajovic B., Dimitrovski A., Fatic N., Malidzan M. and Vukovic M. (2017). **Vacuum erection device in treatment of organic erectile dysfunction and penile vascular differences between patients with DM type I and DM type II**. *The Aging Male: The Official Journal of the International Society for the Study of the Aging Male*, *20*(1), 49–53. https://doi.org/10.1080/13685538.2016.1230601

243. Palmisano F., Boeri L., Cristini C., Antonini G., Spinelli M.G., Franco G., Longo F., Gadda F., Colombo F. and Montanari E. (2018). **Comparison of Infrapubic vs Penoscrotal Approaches for 3-Piece Inflatable Penile Prosthesis Placement: Do We Have a Winner?** *Sexual Medicine Reviews*, *6*(4), 631–639. https://doi.org/10.1016/j.sxmr.2018.03.007

244. Park N.C., Kim T.N. and Park H.J. (2013a). **Treatment Strategy for Non-Responders to PDE5 Inhibitors**. *The World Journal of Men's Health*, *31*(1), 31–35. https://doi.org/10.5534/wjmh.2013.31.1.31

245. Park N.C., Kim T.N. and Park H.J. (2013b). **Treatment Strategy for Non-Responders to PDE5 Inhibitors**. *The World Journal of Men's Health*, *31*(1), 31–35. https://doi.org/10.5534/wjmh.2013.31.1.31

246. Pascual M., de Batlle J., Barbé F., Castro-Grattoni A.L., Auguet J.M., Pascual L., Vilà M., Cortijo A. and Sánchez-de-la-Torre M. (2018). **Erectile dysfunction in obstructive sleep apnea patients: A randomized trial on the effects of Continuous Positive Airway Pressure (CPAP)**. *PloS One*, *13*(8), e0201930. https://doi.org/10.1371/journal.pone.0201930

247. Patel D.P., Pastuszak A.W. and Hotaling J.M. (2019). **Emerging Treatments for Erectile Dysfunction: a Review of Novel, Non-surgical Options**. *Current Urology Reports*, *20*(8), 44. https://doi.org/10.1007/s11934-019-0908-2

248. Pereira E.J., Driver H.S., Stewart S.C. and Fitzpatrick M.F. (2013). **Comparing a combination of validated questionnaires and level III portable monitor with polysomnography to diagnose and exclude sleep apnea**. *Journal of Clinical Sleep Medicine: JCSM : Official Publication of the American Academy of Sleep Medicine*, *9*(12), 1259–1266. https://doi.org/10.5664/jcsm.3264

249. Permpongkosol S., Khupulsup K., Leelaphiwat S., Pavavattananusorn S., Thongpradit S. and Petchthong T. (2016). **Effects of 8-Year Treatment of Long-Acting Testosterone Undecanoate on Metabolic Parameters, Urinary Symptoms, Bone Mineral Density, and Sexual Function in Men With Late-Onset Hypogonadism**. *The Journal of Sexual Medicine*, *13*(8), 1199–1211. https://doi.org/10.1016/j.jsxm.2016.06.003

250. Pickering T.G., Shepherd A.M.M., Puddey I., Glasser D.B., Orazem J., Sherman N. and Mancia G. (2004). **Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents: a randomized controlled trial**. *American Journal of Hypertension*, *17*(12 Pt 1), 1135–1142. https://doi.org/10.1016/j.amjhyper.2004.07.004

251. Pineda M. and Burnett A. L. (2016**). Penile Prosthesis Infections-A Review of Risk Factors, Prevention, and Treatment**. *Sexual Medicine Reviews*, *4*(4), 389–398. https://doi.org/10.1016/j.sxmr.2016.03.003

252. Pinto J.A., Ribeiro D.K., Cavallini A.F. da S., Duarte C. and Freitas G.S. (2016). **Comorbidities Associated with Obstructive Sleep Apnea: a Retrospective Study**. *International Archives of Otorhinolaryngology*, *20*(2), 145–150. https://doi.org/10.1055/s-0036-1579546

253. Pisano F., Falcone M., Abbona A., Oderda M., Soria F., Peraldo F., Marson F., Baral, M., Fiorito C., Gurioli A., Frea B. and Gontero P. (2015). **The importance of psychosexual counselling in the re-establishment of organic and erotic functions after penile prosthesis implantation**. *International Journal of Impotence Research*, *27*(5), 197–200. https://doi.org/10.1038/ijir.2015.17

254. Porst H, Buvat J., Meuleman E., Michal V. and Wagner G. (1998). **Intracavernous Alprostadil Alfadex--an effective and well tolerated treatment for erectile dysfunction. Results of a long-term European study**. *International Journal of Impotence Research*, *10*(4), 225–231. https://doi.org/10.1038/sj.ijir.3900365

255. Porst H. (2021). **Review of the Current Status of Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT) in Erectile Dysfunction (ED), Peyronie's Disease (PD), and Sexual Rehabilitation After Radical Prostatectomy With Special Focus on Technical Aspects of the Different**. *Sexual Medicine Reviews*, *9*(1), 93–122. https://doi.org/10.1016/j.sxmr.2020.01.006

256. Porst H., Burnett A., Brock G., Ghanem H., Giuliano F., Glin S., Hellstrom W., Martin-Morales A., Salonia A. and Sharlip I. (2013). **SOP conservative (medical and mechanical) treatment of erectile dysfunction**. *The Journal of Sexual Medicine*, *10*(1), 130–171. https://doi.org/10.1111/jsm.12023

257. Porst H., Gacci M., Büttner H., Henneges C. and Boess F. (2014). **Tadalafil once daily in men with erectile dysfunction: an integrated analysis of data obtained from 1913 patients from six randomized, double-blind, placebo-controlled, clinical studies**. *European Urology*, *65*(2), 455–464. https://doi.org/10.1016/j.eururo.2013.09.037

258. Poulios E., Mykoniatis I., Pyrgidis N., Zilotis F., Kapoteli P., Kotsiris D., Kalyvianakis D. and Hatzichristou D. (2021). **Platelet-Rich Plasma (PRP) Improves Erectile Function: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial**. *The Journal of Sexual Medicine*, *18*(5), 926–935. https://doi.org/10.1016/j.jsxm.2021.03.008

259. Qin F., Wan, S., Li J., Wu C. and Yuan J. (2018). **The Early Use of Vacuum Therapy for Penile Rehabilitation After Radical Prostatectomy: Systematic Review and Meta-Analysis**. *American Journal of Men's Health*, *12*(6), 2136–2143. https://doi.org/10.1177/1557988318797409

260. Rajagopalan P., Mazzu A., Xia C., Dawkins R. and Sundaresan P. (2003). **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**. *Journal of Clinical Pharmacology*, *43*(3), 260–267. https://doi.org/10.1177/0091270002250604

261. Rastrelli G., Giovannini L., Calogero A.E., Gianfrilli D., Serra E., Pizzocaro A., Giagulli V.A., Motta G., Vancieri G., Sperandio A., Andò S., Selice R., Luca G., Cocchiara F., Canale D. and Maggi M. (2016). **Predictors and clinical consequences of starting androgen therapy in men with low testosterone: results from the SIAMO-NOI registry**. *Journal of Endocrinological Investigation*, *39*(6), 695–708. https://doi.org/10.1007/s40618-016-0461-5

262. Reilly C.M., Lewis R.W., Stopper V.S. and Mills T.M. (1997). **Androgenic maintenance of the rat erectile response via a non-nitric-oxide-dependent pathway**. *Journal of Andrology*, *18*(6), 588–594.

263. Reilly C.M., Stopper V.S. and Mills T.M. (1997). **Androgens modulate the alpha-adrenergic responsiveness of vascular smooth muscle in the corpus cavernosum**. *Journal of Andrology*, *18*(1), 26–31.

264. Rizk P.J., Kohn T.P., Pastuszak A.W. and Khera M. (2017). **Testosterone therapy improves erectile function and libido in hypogonadal men**. *Current Opinion in Urology*, *27*(6), 511–515. https://doi.org/10.1097/MOU.0000000000000442

265. Romero-Otero J., Manfredi C., Ralph D., Osmonov D., Verze P., Castiglione F., Serefoglu E.C., Bozzini G. and García-Gómez B. (2021). **Non-invasive and surgical penile enhancement interventions for aesthetic or therapeutic purposes: a systematic review**. *BJU International*, *127*(3), 269–291. https://doi.org/10.1111/bju.15145

266. Rooney M., Pfister W., Mahoney M., Nelson M., Yeager J. and Steidle C. (2009). **Long-term, multicenter study of the safety and efficacy of topical alprostadil cream in male patients with erectile dysfunction**. *The Journal of Sexual Medicine*, *6*(2), 520–534. https://doi.org/10.1111/j.1743-6109.2008.01118.x

267. Rosen R.C., Cappelleri J.C., Smith M.D., Lipsky J. and Peña B.M. (1999). **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**. *International Journal of Impotence Research*, *11*(6), 319–326. https://doi.org/10.1038/sj.ijir.3900472

268. Rosen R.C., Padma-Nathan H., Shabsigh R., Saikali K., Watkins V. and Pullman W. (2004). **Determining the earliest time within 30 minutes to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study**. *The Journal of Sexual Medicine*, *1*(2), 193–200. https://doi.org/10.1111/j.1743-6109.2004.04028.x

269. Saad F., Aversa A., Isidori A.M., Zafalon L., Zitzmann M. and Gooren L. (2011). **Onset of effects of testosterone treatment and time span until maximum effects are achieved**. *European Journal of Endocrinology*, *165*(5), 675–685. https://doi.org/10.1530/EJE-11-0221

270. Saenz de Tejada I., Kim N., Lagan I., Krane R.J. and Goldstein I. (1989). **Regulation of adrenergic activity in penile corpus cavernosum.** *The Journal of Urology*, *142*(4), 1117–1121. https://doi.org/10.1016/s0022-5347(17)39009-2

271. Salonia A., Adaikan G., Buvat J., Carrier S., El-Meliegy A., Hatzimouratidis K., McCullough A., Morgentaler A., Torres L.O. and Khera M. (2017). **Sexual Rehabilitation After Treatment For Prostate Cancer-Part 2: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015)**. *The Journal of Sexual Medicine*, *14*(3), 297–315. https://doi.org/10.1016/j.jsxm.2016.11.324

272. Salonia A., Burnett A.L., Graefen M., Hatzimouratidis K., Montorsi F., Mulhall J.P. and Stief C. (2012). **Prevention and Management of Postprostatectomy Sexual Dysfunctions Part 1: Choosing the Right Patient at the Right Time for the Right Surgery**. *European Urology*, *62*(2), 261–272. https://doi.org/10.1016/j.eururo.2012.04.046

273. Salonia A., Bettocchi C., Carvalho J., Corona, G., Jones T.H., Kadioglu A., Martinez-Salamanca J.I., Minhas S., Serefoglu E.C., Verze P., Boeri L., Capogrosso P., Cocci A., Dimitropoulos K., Gül M., Hatzichristodoulou G., Kalkanli A., Morgado L.A., Modgil V., Milenkovic U., Russo G., Tharakan T., Darraugh J.A. (2022). **EAU Guidelines on Sexual and Reproductive Health**.

274. Sanda M.G., Dunn R.L., Michalski J., Sandler H.M., Northouse L., Hembroff L., Lin X., Greenfield T.K., Litwin M.S., Saigal C.S., Mahadevan A., Klein E., Kibel A., Pisters L.L., Kuban D., Kaplan I., Wood D., Ciezki J., Shah N. and Wei J.T. (2008). **Quality of life and satisfaction with outcome among prostate-cancer survivors**. *The New England Journal of Medicine*, *358*(12), 1250–1261. https://doi.org/10.1056/NEJMoa074311

275. Sansone A., Romanelli F., Gianfrilli D. and Lenzi A. (2014). **Endocrine evaluation of erectile dysfunction**. *Endocrine*, *46*(3), 423–430. https://doi.org/10.1007/s12020-014-0254-6

276. Satake N., Zhou Q., Morikawa M., Inoue M. and Shibata S. (1995). **Potentiating effect of nicorandil, an antianginal agent, on relaxation in-duced by isoproterenol in isolated rat aorta: involvement of cyclic GMP-inhibitable cyclic AMP phosphodiesterase**. *Journal of Cardiovascular Pharmacology*, *25*(3), 489–494. https://doi.org/10.1097/00005344-199503000-00022

277. Schauer I., Keller E., Müller A. and Madersbacher S. (2015). **Have rates of erectile dysfunction improved within the past 17 years after radical prostatectomy? A systematic analysis of the control arms of prospective randomized trials on penile rehabilitation**. *Andrology*, *3*(4), 661–665. https://doi.org/10.1111/andr.12060

278. Scherzer N.D., Dick B., Gabrielson A.T., Alzweri L.M. and Hellstrom W.J.G. (2019). **Penile Prosthesis Complications: Planning, Prevention, and Decision Making**. *Sexual Medicine Reviews*, *7*(2), 349–359. https://doi.org/10.1016/j.sxmr.2018.04.002

279. Schouten B.W.V, Bosch J.L.H.R., Bernsen R., Blanker M.H., Thomas S. and Bohnen A.M. (2005). **Incidence rates of erectile dysfunction in the Dutch general population. Effects of definition, clinical relevance and duration of follow-up in the Krimpen Study**. *International Journal of Impotence Research*, *17*(1), 58–62. https://doi.org/10.1038/sj.ijir.3901264

280. Schulz R., Bischof F., Galetk, W., Gall H., Heitmann J., Hetzenecker A., Laudenburg M., Magnus T.J., Nilius G., Priegnitz C., Randerath W., Schröder M., Treml M. and Arzt M. (2019). **CPAP therapy improves erectile function in patients with severe obstructive sleep apnea**. *Sleep Medicine*, *53*, 189–194. https://doi.org/10.1016/j.sleep.2018.03.018

281. Scott F.B., Bradley W.E., Timm G.W. (1973)**. Management of erectile impotence. Use of implantable inflatable prosthesis.** *Urology*. 2:80–82. https://doi:10.1016/0090-4295(73)90224-0

282. Scott S., Roberts M. and Chung E. (2019). **Platelet-Rich Plasma and Treatment of Erectile Dysfunction: Critical Review of Literature and Global Trends in Platelet-Rich Plasma Clinics**. *Sexual Medicine Reviews*, *7*(2), 306–312. https://doi.org/10.1016/j.sxmr.2018.12.006

283. Segal R.L., Cabrini M.R., Harris E.D., Mostwin J.L., Bivalacqua T.J. and Burnett A.L. (2013). **Combined inflatable penile prosthesis-artificial urinary sphincter implantation: no increased risk of adverse events compared to single or staged device implantation**. *The Journal of Urology*, *190*(6), 2183-2188. https://doi.org/10.1016/j.juro.2013.06.084

284. Serefoglu E.C., Mandava S.H., Gokce A., Chouhan J.D., Wilson S.K. and Hellstrom W.J.G. (2012). **Long-term revision rate due to infection in hydrophilic-coated inflatable penile prostheses: 11-year follow-up**. *The Journal of Sexual Medicine*, *9*(8), 2182–2186. https://doi.org/10.1111/j.1743-6109.2012.02830.x

285. Shabsigh R., Padma-Nathan H., Gittleman M., McMurray J., Kaufman J. and Goldstein I. (2000). **Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicenter study**. *Urology*, *55*(1), 109–113. https://doi.org/10.1016/s0090-4295(99)00442-2

286. Shamim M.O., Ali Khan F.M. and Arshad R. (2015). **Association between serum total testosterone and Body Mass Index in middle aged healthy men**. *Pakistan Journal of Medical Sciences*, *31*(2), 355–359.https://doi.org/10.12669/pjms.312.6130

287. Shao C., Qi H., Fang Q., Tu J., Li Q. and Wang L. (2020). **Smoking history and its relationship with comorbidities in patients with obstructive sleep apnea**. *Tobacco Induced Diseases*, *18*, 56. https://doi.org/10.18332/tid/123429

288. Sharma R., Oni O.A., Gupta K., Chen G., Sharma M., Dawn B., Sharma R., Parashara D., Savin V.J., Ambrose J.A. and Barua R.S. (2015). **Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men**. *European Heart Journal*, *36*(40), 2706–2715. https://doi.org/10.1093/eurheartj/ehv346

289. Silva G.E., Goodwin J.L., Vana K.D. and Quan S.F. (2016). **Obstructive Sleep Apnea and Quality of Life: Comparison of the SAQLI, FOSQ, and SF-36 Questionnaires**. *Southwest Journal of Pulmonary and Critical Care*, *13*(3), 137–149. https://doi.org/10.13175/swjpcc082-16

290. Sohn M., Hatzinger M., Goldstein I. and Krishnamurti S. (2013). **Standard operating procedures for vascular surgery in erectile dysfunction: revascularization and venous procedures**. *The Journal of Sexual Medicine*, *10*(1), 172–179. https://doi.org/10.1111/j.1743-6109.2012.02997.x

291. Sokolakis I. and Hatzichristodoulou G. (2019). **Clinical studies on low intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic review and meta-analysis of randomised controlled trials**. *International Journal of Impotence Research*, *31*(3), 177–194. https://doi.org/10.1038/s41443-019-0117-z

292. Sopko N.A., Hannan J.L. and Bivalacqua T.J. (2014). **Understanding and targeting the Rho kinase pathway in erectile dysfunction**. *Nature Reviews. Urology*, *11*(11), 622–628. https://doi.org/10.1038/nrurol.2014.278

293. Sperlongano P., Sperlongano S., Foroni F., De Lucia F.P., Pezzulo C., Manfredi C., Esposito E. and Sperlongano R. (2014). **Postoperative hypocalcemia: assessment timing**. *International Journal of Surgery (London, England), 12 Suppl 1*, S95-97. https://doi.org/10.1016/j.ijsu.2014.05.042

294. Stember D.S. and Mulhall J.P. (2012). **The concept of erectile function preservation (penile rehabilitation) in the patient after brachytherapy for prostate cancer**. *Brachytherapy*, *11*(2), 87–96. https://doi.org/10.1016/j.brachy.2012.01.002

295. Stolzenburg J.U., Graefen M., Kriegel C., Michl U., Martin Morales A., Pommerville P. J., Manning M., Büttner H., Henneges C. and Schostak M. (2015). **Effect of surgical approach on erectile function recovery following bilateral nerve-sparing radical prostatectomy: an evaluation utilising data from a randomised, double-blind, double-dummy multicentre trial of tadalafil vs placebo**. *BJU International*, *116*(2), 241–251. https://doi.org/10.1111/bju.13030

296. Suarez-Ibarrola R., Bach T., Hein S., Cocci A., Russo G.I., Herrmann T.R.W., Gratzke C. and Miernik A. (2020). **Efficacy and safety of aquablation of the prostate for patients with symptomatic benign prostatic enlargement: a systematic review**. *World Journal of Urology*, *38*(5), 1147–1163. https://doi.org/10.1007/s00345-019-02959-5

297. Sundaram C.P., Thomas W., Pryor L.E., Sidi A.A., Billups K. and Pryor J.L. (1997)**. Long-term follow-up of patients receiving injection therapy for erectile dysfunction**. *Urology*, *49*(6), 932–935. https://doi.org/10.1016/s0090-4295(97)00079-4

298. Swearingen D., Nehra A., Morelos S. and Peterson C.A. (2013). **Hemodynamic effect of avanafil and glyceryl trinitrate coadministration**. *Drugs in Context, 2013*, 212248. https://doi.org/10.7573/dic.212248

299. Szymanski K.M., Wei J.T., Dunn R.L. and Sanda M.G. (2010). **Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors**. *Urology*, *76*(5), 1245–1250. https://doi.org/10.1016/j.urology.2010.01.027

300. Tajar A., Forti G., O'Neill T.W., Lee D.M., Silman A.J., Finn J.D., Bartfai G., Boonen S., Casanueva F.F., Giwercman A., Han T.S., Kula K., Labrie F., Lean M.E.J., Pendleton N., Punab M., Vanderschueren D., Huhtaniemi I.T. and Wu F.C. W. (2010). **Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study**. *The Journal of Clinical Endocrinology and Metabolism*, *95*(4), 1810–1818. https://doi.org/10.1210/jc.2009-1796

301. Tajar A., Huhtaniemi I.T., O'Neill T.W., Finn J.D., Pye S.R., Lee D.M., Bartfai G., Boonen S., Casanueva F.F.F., Forti G., Giwercman A., Han T.S., Kula K., Labrie F., Lean M.E.J., Pendleton N., Punab M., Vanderschueren D. and Wu F.C.W. (2012). **Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS)**. *The Journal of Clinical Endocrinology and Metabolism*, *97*(5), 1508–1516. https://doi.org/10.1210/jc.2011-2513

302. Tal R., Alphs H.H., Krebs P., Nelson C.J. and Mulhall J.P. (2009). **Erectile function recovery rate after radical prostatectomy: a meta-analysis**. *The Journal of Sexual Medicine*, *6*(9), 2538–2546. https://doi.org/10.1111/j.1743-6109.2009.01351.x

303. Tal R., Jacks L.M., Elkin E. Mulhall J.P. (2011). **Penile Implant Utilization Following Treatment for Prostate Cancer: Analysis of the SEER-Medicare Database**. *Sexual Medicine*, *8*(6), 1797–1804. https://doi.org/10.1111/j.1743-6109.2011.02240.x

304. Tal R., Valenzuela R., Aviv N., Parker M., Waters W.B., Flanigan R.C. and Mulhall J.P. (2009). **Persistent Erectile Dysfunction Following Radical Prostatectomy: The Association between Nerve-Sparing Status and the Prevalence and Chronology of Venous Leak**. *The Journal of Sexual Medicine*, *6*(10), 2813–2819. https://doi.org/https://doi.org/10.1111/j.1743-6109.2009.01437.x

305. Terentes-Printzios D., Ioakeimidis N., Rokkas K. and Vlachopoulos C. (2022). **Interactions between erectile dysfunction, cardiovascular disease and cardiovascular drugs**. *Nature Reviews Cardiology*, *19*(1), 59–74. https://doi.org/10.1038/s41569-021-00593-6

306. Towe M., Huynh L.M., Osman M M., El-Khatib F. M., Andrianne R., Barton G., Broderick G., Burnett A.L., Campbell J.D., Clavell-Hernandez J., Connor J., Gross M., Guillum R., Guise A.I., Hatzichristodoulou G., Henry G.D., Hsieh T.C., Jenkins L.C., Koprowski C., Yafi F.A. (2020). **Impact of Antimicrobial Dipping Solutions on Postoperative Infection Rates in Patients With Diabetes Undergoing Primary Insertion of a Coloplast Titan Inflatable Penile Prosthesis**. *The Journal of Sexual Medicine*, *17*(10), 2077–2083. https://doi.org/10.1016/j.jsxm.2020.07.009

307. Traish A.M., Park K., Dhir V., Kim N.N., Moreland R.B. and Goldstein I. (1999). **Effects of castration and androgen replacement on erectile function in a rabbit model**. *Endocrinology*, *140*(4), 1861–1868. https://doi.org/10.1210/endo.140.4.6655

308. Traish A.M, Toselli P., Jeong S.J. and Kim N.N. (2005). **Adipocyte accumulation in penile corpus cavernosum of the orchiectomized rabbit: a potential mechanism for veno-occlusive dysfunction in androgen deficiency**. *Journal of Andrology*, *26*(2), 242–248. https://doi.org/10.1002/j.1939-4640.2005.tb01091.x

309. Trimmel K., Żebrowska M., Böck M., Stefanic A., Mayer D., Klösch G., Auff E. and Seidel S. (2018). **Wanted: a better cut-off value for the Epworth Sleepiness Scale**. *Wiener Klinische Wochenschrift*, *130*(9), 349–355. https://doi.org/10.1007/s00508-017-1308-6

310. Trost L.W., McCaslin R., Linder B. and Hellstrom W.J.G. (2013). **Long-term outcomes of penile prostheses for the treatment of erectile dysfunction**. *Expert Review of Medical Devices*, *10*(3), 353–366. https://doi.org/10.1586/erd.12.92

311. Trost L.W., Munarriz R., Wang R., Morey A. and Levine L. (2016). **External Mechanical Devices and Vascular Surgery for Erectile Dysfunction**. *The Journal of Sexual Medicine*, *13*(11), 1579–1617. https://doi.org/10.1016/j.jsxm.2016.09.008

312. Tsertsvadze A., Yazdi F., Fink H.A., MacDonald R., Wilt T.J., Bella A.J., Ansari M.T., Garritty C., Soares-Weiser K., Daniel R., Sampson M. and Moher D. (2009). **Oral sildenafil citrate (viagra) for erectile dysfunction: a systematic review and meta-analysis of harms**. *Urology*, *74*(4), 831-836.e8. https://doi.org/10.1016/j.urology.2009.04.026

313. Valerio M., Cerantola Y., Eggener S.E., Lepor H., Polascik T.J., Villers A. and Emberton M. (2017). **New and Established Technology in Focal Ablation of the Prostate: A Systematic Review**. *European Urology*, *71*(1), 17–34. https://doi.org/10.1016/j.eururo.2016.08.044

314. van der Poel H.G., van den Bergh R.C.N., Briers E., Cornford P., Govorov A., Henry A.M., Lam T. B., Mason M.D., Rouvière O., De Santis M., Willemse P.P.M., van Poppel H. and Mottet N. (2018). **Focal Therapy in Primary Localised Prostate Cancer: The European Association of Urology Position in 2018**. *European Urology*, *74*(1), 84–91. https://doi.org/10.1016/j.eururo.2018.01.001

315. Vard Y, Sprecher E. and Gruenwald I. (2000). **Logistic regression and survival analysis of 450 impotent patients treated with injection therapy: long-term dropout parameters**. *The Journal of Urology*, *163*(2), 467–470. https://doi.org/10.1016/S0022-5347(05)67902-5

316. Vardi Y, Appel B., Jacob G., Massarwi O. and Gruenwald I. (2010). **Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction**. *European Urology*, *58*(2), 243–248. https://doi.org/10.1016/j.eururo.2010.04.004

317. Vignatelli L., Plazzi G., Barbato A., Ferini-Strambi L., Manni R., Pompei F., D'Alessandro R. and GINSEN, on behalf of. (2003). **Italian version of the Epworth sleepiness scale: external validity**. *Neurological Sciences*, *23*(6), 295–300. https://doi.org/10.1007/s100720300004

318. Vignozzi L., Filippi S., Morelli A., Ambrosini S., Luconi M., Vannelli G.B., Donati S., Crescioli C., Zhang XH., Mirone V., Forti G. and Maggi, M. (2006). **Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat**. *The Journal of Sexual Medicine*, *3*(3), 419–431. https://doi.org/10.1111/j.1743-6109.2006.00208.x

319. Vignozzi L., Morelli A., Filippi S., Ambrosini S., Mancina R., Luconi M., Mungai S., Vannell G.B., Zhang X.H., Forti G. and Maggi M. (2007). **Testosterone regulates RhoA/Rho-kinase signaling in two distinct animal models of chemical diabetes**. *The Journal of Sexual Medicine*, *4*(3), 620–632. https://doi.org/10.1111/j.1743-6109.2007.00440.x

320. Vinay J., Moreno D., Rajmil O., Ruiz-Castañe E. and Sanchez-Curbelo J. (2021**). Penile low intensity shock wave treatment for PDE5I refractory erectile dysfunction: a randomized double-blind sham-controlled clinical trial**. *World Journal of Urology*, *39*(6), 2217–2222. https://doi.org/10.1007/s00345-020-03373-y

321. Virag R., Zwang G., Dermange H., Legman M. (1981). **Vasculogenic impotence: a review of 92 cases with 54 surgical operations**. *Vascular and Endovascular Surgery*, 15:9–17. https://doi.org/10.1177/153857448101500102

322. Volz-Sidiropoulou E., Pinkawa M., Fischedick K., Jakse G., Gauggel S., Eble M.J. (2008). **FactorAnalysis of the Expanded Prostate CancerIndex Composite in a Patient Group after Primary (External Beam Radiotherapy and Permanent Iodine-125 Brachytherapy) and Postoperative Radiotherapy for Prostate Cancer**. *Current Urology*, *2*(3), 122–129. https://doi.org/10.1159/000189652

323. Walz J., Epstein J.I., Ganzer R., Graefen M., Guazzoni G., Kaouk J., Menon M., Mottrie A., Myers R. P., Patel V., Tewari A., Villers A. and Artibani W. (2016). **A Critical Analysis of the Current Knowledge of Surgical Anatomy of the Prostate Related to Optimisation of Cancer Control and Preservation of Continence and Erection in Candidates for Radical Prostatectomy: An Update**. *European Urology*, *70*(2), 301–311.https://doi.org/10.1016/j.eururo.2016.01.026

324. Wang H., Yuan J., Hu X., Tao K., Liu J. and Hu D. (2014). **The effectiveness and safety of avanafil for erectile dysfunction: a systematic review and meta-analysis**. *Current Medical Research and Opinion*, *30*(8), 1565–1571. https://doi.org/10.1185/03007995.2014.909391

325. Wang R., Burnett A.L., Heller W.H., Omori K., Kotera J., Kikkaw K., Yee S., Day W.W., DiDonato K. and Peterson C.A. (2012). **Selectivity of avanafil, a PDE5 inhibitorfor the treatment of erectile dysfunction: implications for clinical safety and improved tolerability**. *The Journal of Sexual Medicine*, *9*(8), 2122–2129. https://doi.org/10.1111/j.1743-6109.2012.02822.x

326. Wei M., Macera C.A., Davis D.R., Hornung C.A., Nankin H.R. and Blair S.N. (1994). **Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction**. *American Journal of Epidemiology, 140*(10), 930937. https://doi.org/10.1093/oxfordjournals.aje.a117181

327. Williams P., McBain H., Amirova A., Newman S. and Mulligan K. (2021). **Men's beliefs about treatment for erectile dysfunction-what influences treatment use? A systematic review.** *International Journal of Impotence Research, 33*(1), 16–42. https://doi.org/10.1038/s41443-020-0249-1

328. Wilson S. K., Cleves M.A. and Delk J.R. 2nd. (1999). **Comparison of mechanical reliability of original and enhanced Mentor Alpha I penile prosthesis.** *The Journal of Urology, 162*(3 Pt 1), 715–718. https://doi.org/10.1097/00005392-199909010-00022

329. Wittert G. (2014). **The relationship between sleep disorders and testosterone**. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *21*(3), 239–243. https://doi.org/10.1097/MED.0000000000000069

330. Yafi F. A., Jenkins L., Albersen M., Corona G., Isidori A. M., Goldfarb S., Maggi M., Nelson C. J., Parish S., Salonia A., Tan R., Mulhall J.P. and Hellstrom W.J.G. (2016). **Erectile dysfunction**. *Nature Reviews. Disease Primers*, *2*, 16003. https://doi.org/10.1038/nrdp.2016.3

331. Yang R., Huang Y.C., Lin G., Wang G., Hung S., Dai Y.T., Sun Z.Y., Lue T. F. and Lin C.S. (2009). **Lack of direct androgen regulation of PDE5 expression**. *Biochemical and Biophysical Research Communications*, *380*(4), 758–762. https://doi.org/10.1016/j.bbrc.2009.01.144

332. Yaxley J.W. Coughlin G.D., Chambers S.K., Occhipinti S., Samaratunga H., Zajdlewicz L., Dunglison N., Carter R., Williams S., Payton D.J., Perry-Keene J., Lavin M.F. and Gardiner R.A. (2016). **Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study**. *Lancet (London, England)*, *388*(10049), 1057–1066. https://doi.org/10.1016/S0140-6736(16)30592-X

333. Yu B., Wu C., Li T., Qin F. and Yuan J. (2018). **Advances in Gene Therapy for Erectile Dysfunction: Promises and Challenges**. *Current Gene Therapy*, *18*(6), 351–365. https://doi.org/10.2174/1566523218666181004145424

334. Yuan J, Hoang A. N., Romero C. A., Lin H., Dai Y. and Wang R. (2010). **Vacuum therapy in erectile dysfunction--science and clinical evidence**. *International Journal of Impotence Research*, *22*(4), 211–219. https://doi.org/10.1038/ijir.2010.4

335. Yuan J.Q., Zhang R., Yang Z., Lee J., Liu Y., Tian J., Qin X., Ren Z., Ding H., Chen Q., Mao C. and Tang J. (2013). **Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis**. *European Urology*, *63*(5), 902–912. https://doi.org/10.1016/j.eururo.2013.01.012

336. Zargaroff S., Sharma V., Berhanu D., Pearl J.A., Meeks J.J., Dupree J. M., Le B.V., Cashy J and McVary K.T. (2014). **National trends in the treatment of penile prosthesis infections by explantation alone vs. immediate salvage and reimplantation**. *The Journal of Sexual Medicine*, *11*(4), 1078–1085. https://doi.org/10.1111/jsm.12446

337. Zhang X.H., Melman A. and Disanto M.E. (2011). **Update on corpus cavernosum smooth muscle contractile pathways in erectile function: a role for testosterone?** *The Journal of Sexual Medicine*, *8*(7), 1865–1879. https://doi.org/10.1111/j.1743-6109.2011.02218.x

338. Zhang X.H., Morelli A., Luconi M., Vignozzi L., Filippi S., Marini M., Vannell, G.B., Mancina R., Forti G. and Maggi M. (2005). **Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum**. *European Urology*, *47*(3), 409–416; discussion 416. https://doi.org/10.1016/j.eururo.2004.10.021

339. Zhang Y., Ren R., Lei F., Zhou J., Zhang J., Wing Y.K., Sanford L. D. and Tang X. (2019**). Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis**. *Sleep Medicine Reviews*, *45*, 1–17. https://doi.org/10.1016/j.smrv.2019.01.004

340. Zheng W., Chen X., Huang J., Zhang S., Chen T., Zhang L., Li X., Li Q., and Dai J. (2020). **Blood Oxygen Accumulation Distribution Area Index Is Associated With Erectile Dysfunction in Patients With Sleep Apnea Results From a Cross-sectional Study**. *Sexual Medicine*, *8*(1), 36–44. https://doi.org/10.1016/j.esxm.2019.11.001