

TITLE: The Italian Society of Andrology and Sexual Medicine (SIAMS), along with the Italian Society of Endocrinology (SIE), the Association of Clinical Endocrinologists (AME), the Italian Society of Diabetology (SID), the Association of Clinical Diabetologists (AMD), the Italian Society of Internal Medicine (SIMI), the Italian Society of Obesity (SIO), the Italian Society of Metabolism, Diabetes and Obesity (SIMDO), the Italian National Association of Hospital Clinical Cardiologists (ANMCO), the Italian Society of Interventional Cardiology (SICI-GISE), and the Italian Society of Psychopathology (SOPSI) guidelines on diagnosis and management of erectile dysfunction

RUNNING TITLE: Diagnosis and management of erectile dysfunction

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Abstract

Purpose: Erectile dysfunction (ED) is one of the most prevalent male sexual dysfunctions. ED has been in the past mistakenly considered a purely psychosexual symptom by patients. However, an ever-growing body of evidence supporting the role of several organic factors in the pathophysiological mechanisms underlying ED has been recognized.

Methods: The Italian Society of Andrology and Sexual Medicine (SIAMS) commissioned an expert task force involving several other National Societies to provide an updated guideline on the diagnosis and management of ED. Derived recommendations were based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.

Results: Several evidence-based statements were released providing the necessary up-to-date guidance in the context of ED secondary to organic and psychosexual conditions. Many items were related to incorrect lifestyle habits suggesting how to associate pharmacotherapies and cognitive-behavioral therapy in a couple-centered approach. Having the oral therapy with phosphodiesterase type 5 inhibitors as the gold standard along with a number of medical and surgical therapies, new therapeutic or controversial options were also discussed.

Conclusions: These are the first guidelines based on a multidisciplinary approach that involves the most important Societies directly or indirectly related to the field of sexual medicine. This fruitful discussion allowed for a general agreement on several recommendations and suggestions to be reached, which can support all stakeholders in improving couple sexual satisfaction and overall general health.

Keywords: erectile dysfunction, premature ejaculation, sexual desire, obesity, testosterone, phosphodiesterase type 5 inhibitors

INTRODUCTION

After the loss of the penis bone, or *baculum*, during evolution [1, 2], male erectile function shifted from a voluntary, osteo-muscular action, as in the very large majority of mammals, primates included [3], to a psycho-neuro-endocrine and vascular reaction, where the cortical voluntary control, if any, appears to be much more negative than positive [4]. The lack of the baculum and its striated muscular machinery is not the only peculiarity of the human erection (and of the consequent erectile dysfunction, ED); the vessels feeding the high oxygen need of the corpora cavernosa are, in fact, characterized by a very small diameter, much smaller than the coronaries, vessels considered to be at high risk for atherosclerotic degeneration due to this particular geometry [5, 6].

Because of the loss of the baculum, ED may have evolved as a marker of poor phenotypic quality and erectile function in humans appears to be largely, if not totally, will-independent, while it is, at the same time, tremendously age- and lifestyle-dependent [6, 7]. Incorrect behavioral choices are in fact able to affect the ability both to obtain and to maintain an erection in the presence of proper erotic stimuli (which roughly corresponds to the National Institutes of Health's definition of ED) [8]. Interestingly, the main reasons for having ED, i.e. smoking, physical inactivity, poor eating habits and disorders, abuse of alcohol and substances, are also the main causes of the four plus one classical non communicable chronic diseases (NCDs: cardiovascular, metabolic, respiratory and oncological diseases, plus neuropsychiatric diseases, recently added to the list) [6, 9].

Taking into consideration all these findings, it would be easy to consider ED as the perfect (early) biomarker of NCDs, as largely demonstrated by epidemiological studies [6, 7]. In particular, erectile function could be considered as the classical 'canary in the coal mine', thanks to its particular ability to occur earlier, as a consequence of lifestyle mistakes, with respect to the other NCDs [10]. Since the interdisciplinary field of study on NCDs, which looks at the systems of the human body as part of an integrated whole - incorporating biochemical, physiological, and environment interactions - has been named Systems Medicine [11], a new paradigm, named Systems Sexology, which increases and ameliorates the complexity of the traditional bio-psycho-social model [12], seems to be the best approach to ED that results from the complex interactions within the male human body in light of a patient's genomics, behavior and environment [6, 7].

In the majority of cases, ED appears, in fact, as a medical symptom (vascular, endocrine, neurologic, and iatrogenic, frequently with mixed risk factors), more rarely surgical in nature, but with an almost unavoidable psychological and relational comorbidity. For these reasons, diagnosis, management, and follow-up of the patients and of the couples with ED appear relatively complex and deserving of a renewed effort to implement already published guidelines. This is the

aim of these new guidelines of the Italian Society of Andrology and Sexual Medicine (SIAMS) in collaboration with several other National Societies.

METHODS

The SIAMS nominated an expert task force to provide an updated guideline on the diagnosis and management of ED. The project was actively supported by several other National Societies including the Italian Society of Endocrinology (Società Italiana di Endocrinologia, SIE), the Association of Clinical Endocrinologists (Associazione Medici Endocrinologi, AME), the Italian Society of Diabetology (Società Italiana di Diabetologia, SID), the Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD), the Italian Society of Internal Medicine (Società Italiana di Medicina Interna, SIMI), The Italian Society of Obesity (Società Italiana dell'Obesità, SIO), The Italian Society of Metabolism, Diabetes and Obesity (Società Italiana Metabolismo, Diabete, Obesità, SIMDO), the Italian National Association of Hospital Clinical Cardiologists (Associazione Nazionale Medici Cardiologi Ospedalieri, ANMCO), the Italian Society of Interventional Cardiology (SICI-GISE), and the Italian Society of Psychopathology (Società Italiana di Psicopatologia, SOPSI) and a representative member of each Society has signed these Guidelines. According to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [13], here in a series of consensus recommendations have been provided after having widely discussed the best evidence available in PubMed. The GRADE system allows the quality of evidence and the strength of recommendations to be rated, adding value to the clinical advice by using a consistent language and graphical descriptions for standardizing the grading [13]. Concerning the strength of recommendations, the number 1 indicates a strong recommendation and is associated with the terminology “we recommend”; the number 2 denotes a weak recommendation and is associated with the wording “we suggest”. The four level grading of the quality of evidence employs the following graphical descriptions: ⊕○○○ “very low-quality evidence”, ⊕⊕○○ “low quality”, ⊕⊕⊕○ “moderate quality”, and ⊕⊕⊕⊕ “high quality”. Finally, statements, recommendations, or suggestions not supported by direct evidence, but potentially useful for the clinical practice, are marked as “expert opinion” whereas those with high quality evidence for every day clinical activity as “Good clinical practice”.

According to the SIAMS workup and agreement, these Guidelines come from the work of a team of experts on the topic coordinated by the senior author and two members of the SIAMS Guideline Committee. After the revision by the SIAMS Executive Committee and by the Directors of all SIAMS Excellence Centers, these guidelines have then been announced by email and published for two weeks on the SIAMS’s website, siams.info, so that all SIAMS Members could provide further comments and suggest additional minor revisions. Following this last step, the present guidelines

have been submitted to the Journal of Endocrinological Investigation for the normal process of international peer reviewing.

EPIDEMIOLOGY AND RISK FACTORS

Evidence supporting that a specific ED case is due to a single and unique etiological factor is scarce and not supported by common clinical practice. For this reason, in defining the well-known mechanisms related to ED, we discourage the use of the term “etiologies”. The term “risk factors” is preferred, also considering that there are frequently multiple factors in the same patient (see also Table 1).

Epidemiology

Recommendation #1. *We recommend considering erectile dysfunction as a common male disorder whose incidence and prevalence are strongly associated with age and health status (1 0000).*

Evidence

ED is a common medical disorder in men whose incidence and prevalence increases with age and is associated with poorer general health and presence of comorbidities (see below) [14]. The crude incidence of ED varies widely among studies and, based on the age of the studied cohorts, ranges from 4 to 66 cases per 1,000 men/year [14-17]. Similarly, the prevalence of ED varies based on the age of the enrolled subjects [14]. The Massachusetts Male Ageing Study (MMAS) showed a combined prevalence of mild to moderate ED of 52% in men aged 40–70 years, and ED was strongly related to age, health status and emotional factors [18]. Conversely, the European Male Ageing Study, the largest European multicentre population-based study of ageing men (40–79 years), reported a prevalence of ED ranging from 6% to 64%, depending on different age subgroups and increasing with age, with an average prevalence of 30% [19]. The prevalence of ED seems higher in the United States and Eastern and South-Eastern Asian countries, compared to Europe or South America [20]. The prevalence of ED varies also according to ethnicity. Hispanic men had increased odds of moderate-severe ED, whereas Black men were less likely to report moderate to severe ED. The prevalence of ED among different racial and ethnic groups is likely the result of complex phenomena and depends upon the interplay of socioeconomic, demographic, cultural, and lifestyle characteristics [14]. Despite few data on the epidemiology of ED in men younger than 40 years, a very recent study reported a prevalence of 11.3% of mild ED and 2.9% of moderate-to-severe ED in a sample of 2660 sexually active men in the age range 18-31 years [21].

Remarks

We highly value considering ED as a marker of general male health status and as an expression and part of many comorbidities, rather than a manifestation of ageing. Studies involving male populations older than 70 years are limited, resulting, therefore, in an underestimation of the problem. Similarly, ED has scarcely been evaluated in men younger than 40 years, generating the false assumption that this symptom is almost unheard of in young people [14].

Risk factors

Several systemic conditions as well as organic, relational and intrapsychic factors can contribute to the development of ED (Table 1). Moreover, ED is frequently comorbid with other sexual dysfunctions, either in the patients and/or in the partner, which may amplify the erectile failure in subclinical forms (see below) into an overt ED.

Systemic risk factors

Recommendation #2. *We recommend investigating sexual function and ruling out erectile dysfunction in all patients with systemic diseases especially in those with organ failure (Good clinical practice).*

Evidence and remarks

Systemic diseases characterized by organ failure (such as end-stage renal diseases [22] and liver cirrhosis[23], as well as those conditions related to systemic inflammation such as HIV [24, 25] or to some rheumatic and/or autoimmune diseases [26-29]) are frequently associated with ED, couple impairment and reduced quality of life. Similarly, considerations can be drawn for some malignancies with long life expectancy such as lymphomas and testis cancers[30]. Finally, emerging evidence has documented that ED can be considered a long-term consequence of coronavirus disease 2019 (COVID-19) infection [31-33]. In all the aforementioned problems, ED is the result of the interaction between multiple risk factors which will be analyzed in detail in the following sections. However, we want to emphasize that frequently sexual function and ED, in particular, are often poorly investigated, if not ignored, in the vast majority of cases. Some evidence indicates that an improvement of sexual function can ameliorate couple intimacy quality, and quality of life, as well as diseases-related distress [22, 23, 28, 30].

Cardiovascular and respiratory risk factors

Arterial hypertension

Recommendation #3. *We recommend investigating erectile dysfunction in individuals with arterial hypertension since it is strongly associated with hypertension duration and severity (100000), and it might be related to the use of some anti-hypertensive medications (100000).*

Evidence

Around 30-45% of adults are affected by arterial hypertension, and the prevalence increases with age, affecting more than 60% in people aged >60 years [34]. The association between arterial hypertension and ED is very frequent and up to seven times higher when compared to that observed in the general population [35]. Moreover, in hypertensive patients, ED is usually more severe than in normotensive people [35]. Considering this close association, information on ED must be regularly collected in all hypertensive patients. ED is effectively treated by phosphodiesterase-5 inhibitors (PDE5i), also in hypertensive subjects, but this class of medication is absolutely contraindicated if concomitantly administering nitrates, and relatively contraindicated in treatment with alpha-blockers [36].

Remarks

It should be recognized that several classes of anti-hypertensive drugs have been associated with a higher risk of ED although only few placebo RCTs have correctly investigated the role of these medications in erectile function (see below) [37].

Cardiovascular diseases

Recommendation #4. *We recommend checking for symptoms of coronary artery disease in all patients with erectile dysfunction at each visit and evaluating the cardiovascular risk profile using cardiovascular algorithms such as SCORE2 or SCORE2-OP (Systematic Coronary Risk Estimation 2 and Systematic Coronary Risk Estimation 2-Older Persons) (1 00000).*

Evidence

Much evidence has clearly demonstrated that ED is frequently comorbid in patients with cardiovascular diseases (CVD) since the two conditions often share the same risk factors [6]. In addition, data from longitudinal studies performed either in symptomatic patients or in the general population have shown that ED could represent an early sign of forthcoming Major Adverse Cardiovascular Events (MACE) [6]. Hence, the presence of sexual symptoms must be ruled out in all patients with documented CVD and subjects with ED should be adequately investigated to stratify their cardiovascular (CV) risk since the appearance of symptoms allows for a valuable time window [2-5 years] for earlier modification of associated risk factors and potentially an improvement in outcomes [6].

Several risk engines have been developed for the quantification of CV risk profile. The Framingham risk engine represents the most used risk prediction equation, originally developed in the United States. However, its application in European populations showed an overestimation of CV risk profile [38]. Conversely, Systematic Coronary Risk Estimation 2 and the Systematic Coronary Risk Estimation 2-Older Persons (SCORE) chart [39] (<https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts>) have demonstrated better utility in European subjects, including Italians [40]. The SCORE2 and SCORE2-OP charts estimate an individual's 10-year risk of fatal and non-fatal CVD events (myocardial infarction, stroke) in apparently healthy people aged 40-69 years and ≥ 70 years with risk factors that are untreated or have been stable for several years. Lifetime benefit estimation of risk factor treatment, e.g. with the LIFE-CVD (LIFETIME.PerspectiveCardioVascular Disease) lifetime model, can facilitate the communication of treatment benefits [40].

Remarks

The SCORE algorithm should not be used for persons with established atherosclerotic CVD, diabetes mellitus (DM), chronic kidney diseases, and familial hypercholesterolemia, categories associated with moderate to very high CV disease risk [39]. It is important to recognize that not only traditional CV risk factors, but also unconventional components related to relational and intrapsychic determinants can contribute to the CV risk stratification of ED subjects [41-43]. The identification and the early recognition of these comorbid factors can allow a specific prevention program based on lifestyle modifications and optimization of the concomitant chronic diseases to be promoted, which might help not only in improving ED treatment outcomes but also in ameliorating couple fitness and decreasing the “residual CV risk” thus improving CV risk prevention (see below).

Chronic obstructive pulmonary disease and sleep apnea

Recommendation #5. *We suggest investigating erectile dysfunction in all patients with chronic obstructive pulmonary disease and obstructive sleep apnea (2 0000).*

Evidence and remarks

Chronic obstructive pulmonary disease (COPD) is a frequent condition resulting from long-term exposure to harmful particles or gases (mainly smoking) which has been reported as the third leading cause of death globally [44]. ED is a frequent complication of COPD with a reported prevalence ranging from 72% to 87% of cases [44]. A recent meta-analysis including 31 studies, for a total of 1187 patients with COPD, and 224 age-matched, non-COPD controls, showed a pooled prevalence of ED in 74% (95% CI: 68-80%) of patients with COPD, compared to 56% (37-73%) observed in controls [45]. Similarly, another meta-analysis involving 58,307 subjects documented an up to 3-fold increased risk of moderate to severe ED in subjects with COPD when compared to controls [46]. Obstructive sleep apnea (OSA) is another common respiratory problem frequently associated with ED [47]. In the latter condition, ED prevalence increases as a function of age and body mass index (BMI) but it is also closely related to the apnea-hypopnea index which reflects OSA severity. A combination of vascular and hormonal (reduced testosterone, T, levels) factors represents the main pathogenetic determinants in both COPD and OSA, although the chronic reduced systemic oxygenation, as well as relational and intrapsychic factors, can contribute to the development and to the maintaining of ED in these subjects. Despite the aforementioned evidence, ED and sexual function is poorly investigated in COPD and OSA. Accordingly, although the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) guidelines recommend the assessment of the state of sexual activity in COPD men, they do not contain any information regarding how to evaluate or manage the problem [44].

Metabolic risk factors

Obesity

Recommendation #6. *We recommend investigating sexual function in all male patients with obesity (1 0000).*

Evidence

A large body of evidence has shown that obesity is a major independent risk factor for ED [6, 48-50] and that the incidence rate of ED increases proportionally to the degree of obesity [51, 52]. Among patients with ED, obesity has also been reported as a further risk factor for CVD [53]. It is conceivable that the higher prevalence of ED in obese subjects may be related to hypogonadism [54]; however, other pathophysiological mechanisms are also involved, including endothelial dysfunction, insulin resistance, psychological factors and physical inactivity [55]. Several randomized controlled trials (RCTs) on obese people have shown that lifestyle changes aimed at weight loss significantly improved erectile function [48, 49, 51], further supporting a cause-effect relationship between obesity and ED. This was also confirmed by prospective cohort studies of obese men undergoing bariatric surgery who significantly improved their T levels and sexual function upon the intervention [56].

Diabetes mellitus

Recommendation #7. *We recommend investigating erectile dysfunction in all patients with diabetes mellitus since it is strongly associated with diabetes duration, metabolic control and coexistence of other diabetic complications (1 0000).*

Evidence

ED prevalence is markedly increased in men with diabetes mellitus (DM), but with a huge variability mainly due to the clinical features of the studied populations. According to a meta-analysis, overall prevalence is 52.5% with a clear difference between type 1 (37.5%) and type 2 (66.3%) DM; compared to healthy controls, people with diabetes had a 3.62 odds ratio of having ED [57]. Also incidence is 2-3 folds higher than in general age-matched populations [58]. Even when the same diagnostic tool is used, (i.e. International Index of Erectile Function; IIEF), prevalence can range from 35 to 90% [59]. Age, duration of the disease, metabolic control and concomitant chronic DM complications seem to be the major factors influencing prevalence and severity of ED in DM [59-61]. In the first large cross-sectional study performed in Italy on about 10,000 subjects, ED prevalence, assessed by means of an interview, was 35.8% and it was clearly influenced by age, diabetes duration, metabolic control, other chronic complications, and smoking [58]. More recently, in a population with newly diagnosed type 2 DM (TDM2), overall ED prevalence was 60% and its severity, assessed by means of IIEF-5, was associated with age, HbA1c levels, arterial hypertension, dyslipidemia and depression

[60]. Due to the delay between TDM2 onset and its diagnosis, ED prevalence is high (43.3%) also in newly diagnosed subjects [62] and it is associated with hypogonadism, depressive symptoms and CV risk [60].

Remarks

Despite available evidence, ED in DM is still underestimated in routine clinical practice and consequently under-treated. This is even more important when considering that, in addition to sexual dysfunction, ED is associated with other conditions such as depression and CVD, which, all together, have a deeply negative impact on quality of life and life expectancy in male DM subjects [63].

Dyslipidemia and Gout

Recommendation #8. *We recommend investigating erectile dysfunction in all patients with dyslipidemia (1 0000) and gout (1 0000).*

Dyslipidemia

It is well known that dyslipidemia is clearly associated with MACE, [64]. Considering that ED is another well-known risk factor for MACE [6], associations between the two conditions have been thoroughly investigated.

Evidence

An association between ED and dyslipidemia has been evident since the last decade of the past century, thanks to the seminal study of Feldman et al. [18] in a cohort of 1290 men enrolled in the MMAS. In fact, in the cross-sectional analysis of the MMAS cohort, the probability of ED ranged from 7 to 25% when high density lipoprotein cholesterol (HDL-C) decreased from 90 to 30 mg/dL [18]. In the same years, Wei et al. [65] published longitudinal results from a cohort of 3,250 Texan men without ED at study entry. After a mean of 22 months of follow-up, a 39 mg/dL increase in total cholesterol (TC) or in HDL-C was associated with a change of 1.32 [1.04-1.668] and 0.38 [0.18-0.8] times in the risk of ED, even after adjusting for other ED determinants. In particular, a TC>240 mg/dL or a HDL-C<30 mg/dL double the risk of ED [65]. Results were also confirmed in a recent study where high low density lipoprotein cholesterol (LDL-C)/HDL-C and low HDL-C were able to predict arteriogenic ED, as assessed by dynamic peak systolic velocity (PSV) at penile color Doppler ultrasonography (PCDU) in a small series of ED patients (n=84) [66]. In a larger series of unselected ED patients (n=2160), it was reported that high TC and triglyceride levels and low HDL-C were all associated with a reduced dynamic PSV [67]. However, when all these lipids were introduced in an age-adjusted

multivariate model, only high TG levels retained significant association with impaired penile blood flow [67]. In a longitudinal study on a fraction of the above cohort, high triglyceride levels were also able to predict MACE [67]. Finally, in a study on patients with diabetes mellitus, HDL-C had a significant correlation with number of erectile episodes during the night, as documented by nocturnal penile tumescence studies such as Rigiscan [68]. A causal relationship between high lipids and ED is supported by intervention studies. Two meta-analyses investigating the effect of treating dyslipidemia on erectile function suggest that statin therapy is associated with a clinically meaningful increase by 3.3 points on the IIEF erectile function domain (IIEF-EFD) score [69] and that the addition of statins to sildenafil improves the response to sildenafil itself [70].

Remarks

ED is now considered a harbinger of MACE and it is now included in the algorithms of risk prediction of CV events [70]. Considering that lipid-lowering medications can substantially decrease CV risk and even ameliorate ED [69, 70], it is imperative for clinicians dealing with ED to obtain a full lipid profile in any ED patients and to treat any dyslipidemia accordingly.

Gout

The association between gout, the most common crystal arthropathy, and sexual dysfunction has often been investigated by studies in recent decades. Awareness of this association is frequently lacking and the pathogenetic mechanisms have only partially been identified.

Evidence

A recent meta-analysis [71] evaluating the risk of ED in subjects with gout indicates an overall statistically significant increased risk of ED in subjects with gout (RR=1.2; 95%CI=1.1-1.31). A subgroup analysis indicates that this increased risk was apparent only in longitudinal cohort studies (n=5, RR=1.22; 95%CI=1.12-1.32) but not in the three cross-sectional studies investigated. Similar results were derived from a previous meta-analysis involving a lower number of studies [72]. In one of the aforementioned longitudinal studies conducted in Taiwan, it was also observed that in subjects with gout and without comorbidities treated for more than three months with urate-lowering agents, the risk of developing ED was similar to that of a control cohort without gout [73].

Remarks

Having gout there is a 20% increased risk of developing ED, even after adjusting for possible confounders, including comorbidities. Considering that hyperuricemia is the underlying condition favoring gout development and that hyperuricemia is associated with endothelial dysfunction and CVD [74], it is obvious that known or even unknown comorbidities might favor ED development [75]. Finally, the couple, being in a stable relationship, may have a positive “anti-inflammatory” role in modifying incorrect lifestyles leading to gout and to other metabolic risk factors producing ED [76].

Hormonal disorders

Recommendation #9. *We recommend investigating sexual function in male patients with low testosterone. (10000).*

Recommendation #10. *We suggest considering the investigation of sexual function in other endocrine conditions such as thyroid, adrenal and pituitary diseases (2 0000).*

Evidence

The importance of T for the maintenance of normal sexual function is well established, and reduced serum total T levels ($T < 12$ nmol/L) represent a clear risk factor for ED; moreover, in men with normal serum total T levels, calculated free T (cFT) correlates with the severity of ED [77-79]. Data from the EMAS study clearly outlined that total T is positively associated with overall sexual function, and that cFT is associated with ED and masturbation frequency [80]. Moreover, patients with low cFT, even in the presence of normal serum total T levels, reported an impairment in erectile function, orgasmic function and sexual functioning as evaluated with IIEF-15, compared to men with normal total T and cFT [81]. Similar results have been reported in men consulting for sexual dysfunction [82].

Hyperprolactinemia may represent a rare cause of ED [83, 84]. Severe hyperprolactinemia (prolactin, PRL > 35 ng/ml) is associated with ED mainly through an indirect mechanism that depends on the reduction of T levels [83, 84]. In addition, PRL might have a deleterious effect on erection acting at a central level through a modulation of dopaminergic neuron activity within the hypothalamus [83, 84]. From preclinical studies in rats, PRL can have a negative action on male sexuality acting also on the molecular machinery leading to penile erection [83, 84]. Accordingly, RCTs show that ED induced by hyperprolactinemia in patients with prolactinomas does not regress with T replacement therapy

(TRT) alone, supporting a direct role of PRL itself and/or its central regulator dopamine, as an independent risk factor for ED [85, 86].

Thyroid diseases are frequent medical conditions often associated with male sexual dysfunction [84, 87-89]. Some evidence, however, has suggested that ED is mainly related to hyperthyroidism, whereas the association with hypothyroidism is less clear [90]. Accordingly, the normalization of thyroid hormones is associated with a significant improvement of erectile function, whose underlying mechanisms seem to depend on an impairment of nitric oxide (NO)-cyclic guanosine-monophosphate (cGMP)-dependent relaxation of corpora cavernosa [84].

In men with autoimmune Addison's disease, corticoid deficiency is positively associated with ED, and erectile function is restored in the recovery phase of the disease [84]. In Cushing's syndrome, sexual dysfunctions are frequent, including ED, linked both to a hypogonadism induced by excess glucocorticoids and to a direct effect of testicular and endothelial damage induced by excess glucocorticoids [84, 91], as well, very likely, to the body modifications impacting self-esteem.

Remarks

Whereas the association between low T and ED is well documented, the role played by other hormones in regulating male sexual function is still limited and more studies are advisable to better understand this aspect.

Neurological disorders

Recommendation #11. *We suggest investigating erectile function in all patients with central and peripheral neurological diseases potentially affecting male sexual response (2 0000).*

Evidence

Several central and peripheral neurological diseases have been associated with an increased risk of ED. Spinal cord injury, often a consequence of crashes or falls, are frequently characterized by some type of erection difficulty (i.e., psychogenic or reflexive), depending on the level of spinal damage. However, erectile responses often are not sufficiently predictable, rigid, or long-lasting enough for satisfactory sexual intercourse [92].

Dopamine pathway is crucial for the central regulation of male sexual function. Hence, although hypersexuality is rarely reported in untreated Parkinson's disease, the presence of sexual dysfunctions, including reduced libido and ED, are quite common in these patients [93]. Other central neurological diseases frequently associated with an increased risk of ED are multiple system atrophy [94], multiple sclerosis [95] and epilepsy [96]. Finally, peripheral nervous system disorders, especially those involving the autonomic nervous system, can cause ED as well as ejaculatory problems, the severity of which depends upon the degree of involvement of the innervation of genital organs [97].

Urological disorders

Lower Urinary Tract Symptoms

Recommendation #12. *We recommend screening patients with erectile dysfunction with the International Prostatic Symptom Score and patients with benign prostate obstruction with the International Index of Erectile Function (IIEF).*

Evidence

ED is a risk factor for Lower Urinary Tract Symptoms (LUTS) and vice-versa. Hence, the two conditions are often associated, most probably because they share common pathogenetic mechanisms. In a sample of 1410 United States (US) men aged 18 to 59 years, a three-fold increased risk of having ED in subjects with LUTS was first described [98]. Later on, similar figures were confirmed in European [19] and Asian cohorts ([99], (see for review [100]). It is reasonable to conceive that ED and benign prostate obstruction (BPO)/LUTS are associated because they share similar risk factors, including metabolic disorders and hormonal imbalances [100, 101]. Possible shared pathogenetic mechanisms include: alteration of the NO-cGMP pathway, enhancement of RhoA-Rho-kinase (ROCK) signaling, autonomic hyperactivity and pelvic atherosclerosis [102].

Remarks

Considering the common association between BPO/LUTS and ED, it is interesting to understand whether or not treating one condition improves the other one. However, the impact of intervention studies in any of the two conditions, to determine the effects on the other one, is difficult to evaluate because medical treatments for LUTS can improve or deteriorate ED and vice versa. For example, phosphodiesterase type 5 inhibitor (PDE5i) can improve LUTS [103] and

5 α reductase inhibitors, used for LUTS management, can cause ED [104]. Lessons from non-medical interventions are therefore interesting. Some surgical interventions on BPO can indeed improve IIEF scores, although their effects are based more on the improvement in quality of life than on altering the molecular mechanism underlying ED [105]. Hence, as stated before, it is conceivable that the two conditions are associated because they share common pathogenetic mechanisms and not because of a causal relationship [102].

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)

Recommendation #13. *We suggest investigating erectile dysfunction in all patients with CP/CPPS (2 ØØØØ).*

Evidence

CP/CPPS is a very common urologic problem with a tremendous negative impact on patient quality of life [106, 107]. A recent meta-analysis including 24 studies and 11,189 men reported a prevalence of ED up to 33% [106]. Specific underlying mechanisms have not been completely clarified but vascular, endocrine, neurological and psychological factors have been considered [106].

Peyronie's Disease (PD)

Recommendation #14. *We suggest ruling out erectile dysfunction in all patients with Peyronie's Disease (2 ØØØØ).*

Evidence

It was often postulated that a sexual trauma, due to an inappropriate erection for sexual penetration, might have an important role in PD pathogenesis, causing fibrin accumulation in the penile tunica albuginea and an inflammatory reaction, finally leading to a discrete penile fibrosis and plaque formation [108]. In ED subjects, the prevalence of PD was estimated around 10%, which is not so different from that described in the general population [108]. Hence, having ED does not apparently increase the risk of PD, although PD is often associated with an impaired erection due to either mechanical or psychological issues [108]. Animal and cellular models have indicated that activating the NO pathway can ameliorate fibrosis and isolated clinical studies have shown that a daily, low-dose tadalafil administration can ameliorate scar formation in the initial phase of the disease [35].

Toxicological and iatrogenic risk factors

Substances/Drugs Abuse

Recommendation #15. *We recommend considering the use of psychotropic drugs (e.g.: opioid, amphetamine, methamphetamine, and cannabis) as a possible risk factor for erectile dysfunction (10000).*

Recommendation #16. *We suggest specifically investigating the presence of long-term use of illicit psychotropic drugs in patients with inadequate response to treatment of erectile dysfunction (20000).*

Evidence and remarks

ED is demonstrated to be associated with the use of opioids [109], amphetamine[110], methamphetamine [111], and cannabis [112]. However, the association between ED and substance use disorder (SUD) is not solid, due to the lack of robust studies. Therefore, it is necessary to replicate the current findings and broaden the current evidence for such an association. Due to the nature of SUD (often undisclosed and sometimes hidden for several years), the type of assessment of ED (based almost exclusively on patient- and couple-reported experience), and the poor quality of the available studies, it cannot be excluded that real rates of ED associated with the use of illicit drugs may be higher than those found in the current scientific literature. Finally, in patients with ED presenting with a “resistant-to-treatment” condition to conventional therapy for ED, the presence of SUD, or withdrawal after acute or chronic use of any addictive substance, should be considered.

Iatrogenic medical

Recommendation #17. *All patients treated with anti-androgenic drugs must be informed about possible negative effects on erectile function (Good clinical Practice).*

Recommendation #18. *We recommend investigating erectile function in all men treated with most antidepressants or antipsychotic medications (10000).*

Recommendation #19. *We suggest investigating sexual function in young patients with a history of previous treatment with drugs affecting the serotonergic pathway or the conversion of testosterone to dihydrotestosterone (20000).*

Recommendation #20. *We suggest against using beta-blockers as a first line therapy in patients with de-novo diagnosed arterial hypertension, if no specific cardiological indications are present (2000).*

Evidence

As reported above, T is the key regulator of male sexual response. Hence, the occurrence of ED in men treated with drugs with anti-androgenic effects is not surprising. Accordingly, a recent meta-analysis of the available studies documented that androgen deprivation therapy in patients with prostate cancer resulted in a 5- to 6-fold increased risk of reduced libido and in a 3-fold increased risk of ED [113, 114]. Similar observations can be drawn when 5-alpha reductase inhibitors are considered, in fact they were associated with an up to 70% increased risk of ED [104].

Since the mechanism of action of several antipsychotic or antidepressant medications is based on the modulation of serotonergic (increasing) and dopaminergic (decreasing) transmission, the use of these drugs is frequently associated with the development of ED or with male sexual function impairment [115]. Among anti-psychotics, quetiapine, ziprasidone, perphenazine, aripiprazole and brexpiprazole (with the last two associated with the lowest impact on sexual life) have been related to lower rates of sexual dysfunction (16–27%), when compared to olanzapine, risperidone, haloperidol, and clozapine (40–60%), probably as a consequence of their lower effect on PRL increase [116]. Among antidepressants, bupropion, a norepinephrine and dopamine reuptake inhibitor, has shown limited or no influence on sexual dysfunction, both when depressed population and healthy volunteers were considered [115]. Similarly, antidepressants with a mixed (serotonergic and norepinephrine/ dopamine) mechanism of action were associated with lower sexual side effects when compared to pure serotonin-reuptake inhibitors (SSRI) [117]. Among pure SSRI, vortioxetine is a serotonin transporter blocker also interacting with several serotonergic receptors (antagonist for the 5-HT₃ and 5-HT₇ receptors, partial agonist for 5-HT_{1B}, and agonist for 5-HT_{1A}). Due to these peculiar properties, vortioxetine has shown lower sexual side effects when compared to other SSRIs [115, 118].

Persistent sexual dysfunction after discontinuation of serotonin reuptake inhibiting antidepressants, 5 alpha-reductase inhibitors and isotretinoin has been reported and named post-SSRI sexual dysfunction (PSSD), post-finasteride syndrome (PFS), and post-retinoid sexual dysfunction (PRSD), with anhedonia, sexual anesthesia and ED as frequent but not unique symptoms referred by the patients. These syndromes, which appear more common in young males, despite a lack of specific treatment, deserve careful sexological, medical, and psychiatric attention [119].

Several anti-hypertensive medications have been often inappropriately associated with ED. Among them, β -blockers and thiazide diuretics were those with the highest incidence of ED [37]. However, it should be emphasized that the vast majority of the reports come from observational and uncontrolled trials limiting the evidence. Recently, Farmakis et al., [37] performed a network meta-analysis exploring the role of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, calcium channel blockers, and thiazide diuretics on erectile function when compared to each other and to placebo. By including 25 studies and 7784 patients, they reported no significant differences in erectile

function among the aforementioned antihypertensive classes in pairwise comparisons. Similar data were derived when placebo RCTs were considered. In addition, when different classes of β -blockers were analyzed, nebivolol resulted in less significant effects on erectile function when compared to non-vasodilatory β -blockers but not when placebo was considered [37]. In line with these data, almost 20 years ago, Silvestri et al., [120], in a well-designed RCT, documented that the negative effects related to the use of β -blockers on erectile function are strongly influenced by the knowledge and prejudice about their related side effects commonly called “nocebo effects”.

Remarks

As reported above, a recent meta-analysis of the available RCTs did not confirm the frequently reported increased risk of ED related to the use of β -blockers. However, it is important to recognize that the quality of the available evidence is limited and the same authors recognized that the risk of bias was high or at least concerning in the majority of studies included in their analysis [37]. Hence, it is our opinion that β -blockers should not be used as a first line therapy especially in young *de novo* subjects with arterial hypertension and low CV risk.

Iatrogenic surgical

Recommendation #21. *We recommend investigating sexual function in all patients treated with pelvic surgery for malignancies (10000).*

Evidence and remarks

ED is a frequent complication of pelvic surgery performed for the treatment of several malignancies. Both neurological and vascular problems have been suggested to play a pathogenetic role. Radical prostatectomy for prostate cancer is one of the most common causes of surgical iatrogenic ED with an estimated prevalence at 12 and 24 months ranging from 54% to 90% and 63% to 94%, respectively [121, 122]. Similarly, a high frequency of ED has been reported in subjects treated for bladder and colorectal cancers [123, 124]. The use of nerve-sparing techniques and robotic surgery can improve surgery outcomes by reducing its complication, including sexual problems [125-127]. Conversely ED is generally transitory and affects about 25% of patients treated with retroperitoneal lymph node dissection for testis cancer [128]. Much evidence suggests that an early approach to ED after pelvic surgery can improve long-term

outcomes. However, so far, no specific medical, mechanical, physical or mixed approach has clearly documented an advantage over the others [102].

Psychiatric, psychological and relational risk factors

Psychiatric disorders

Recommendation #22. *We recommend considering psychiatric disorders (such as schizophrenia, bipolar disorders, post-traumatic stress disorder) as risk factors for erectile dysfunction (10000).*

Recommendation #23. *We recommend considering anxiety and depression as independent predictors of erectile dysfunction and its severity. (10000).*

Evidence

Both generalized or constitutive and reactive anxiety and depression are highly prevalent in patients with ED [129, 130]. This association is of particular relevance especially in young men, in whom anxiety and depression are among the main risk factors for ED [131-133]. The greater the severity of ED, the greater the prevalence and severity of anxiety and depression. This relationship does not demonstrate which condition plays the causative reciprocal role. In men with diabetes and depression, a significantly higher prevalence of ED is observed [60, 134], with depressive symptoms showing an independent and positive association with the severity of ED [135]. Moreover, it has been demonstrated that young people in the early stages of psychosis have higher rates of ED [136] and that men suffering from bipolar disorder and post-traumatic stress disorder may also have a higher risk of ED [137, 138], not associated with the use of psychotropic medications.

Remarks

The use of screening tools for erectile function in men affected by psychiatric disorders, particularly those young people with early stage psychosis, can improve the detection of ED [139]. The great occurrence of anxiety and depression among patients with ED needs an early diagnosis and adequate treatment of these psychopathological conditions, especially among younger patients with ED, patients with a longer duration of ED, and patients with ED associated with

comorbid chronic medical disorders. Finally, in the treatment of anxiety or depressive disorders, the choice of psychotropic drugs with a lower risk of worsening ED is strongly advocated (see above).

Intrapsychic and relational risk factors

Recommendation #24. *We recommend considering intrapsychic factors as major risk factors for developing and maintaining erectile dysfunction (1 ØØØØ).*

Recommendation #25. *We recommend considering relational and marital factors as major risk factors for developing and maintaining erectile dysfunction (1 ØØØØ).*

Recommendation #26. *We recommend considering non-organic and organic risk factors always jointly and in their entirety (Good Clinical Practice).*

Evidence

A number of intrapsychic and relational factors have been consistently related to ED [129, 140-142]. Interestingly, many of them can promote ED, acting as non-organic risk factors, or they can be a consequence of the ED, playing a role in maintaining and amplifying the sexual dysfunction. In many cases, there are no diagnostic instruments to ascertain if a given psychological symptom is causing or is caused (by) the ED. This admission of impotence in determining the causal relationship must not prevent the clinician from exploring the psycho-relational aspects in all cases of ED. The main psychological factors are *i*) personality [143]; *ii*) depression and other mood disturbances [130], *iii*) anxiety (particularly performance anxiety) [144], and *iv*) relationship factors [142].

Sexual risk factors

Hypoactive Sexual desire

Recommendation #27. *We recommend investigating sexual desire in subjects with erectile dysfunction, because the two conditions are often comorbid (1 ØØØØ).*

Evidence

Reduced libido was comorbid with ED in almost 40% of cases, as derived from a large series (n=3714) of patients complaining of sexual dysfunctions studied at the University of Florence [145]. Interestingly, a latter survey indicated that having any form of libido reduction (n=1341), i.e. with or without hypogonadism or psychiatric derangements, is associated with a 2-3 fold increased risk of having severe ED [145]. However, treating ED with PDE5i is not associated with a significant improvement in sexual desire, not only in the male patient, but also in the female partner [146, 147]. No information is available on the effect of treating low libido on erectile function, most probably because specific medications for the treatment of low desire are not available [148].

Remarks

The items concerning sexual desire in several questionnaires have not yet been validated to explore low libido [149]. The population included in the trials were, in fact, not affected by low desire.

Premature ejaculation

Recommendation #28. *We suggest, in patients with loss of control of erection and ejaculation, addressing the erectile function before any therapeutical attempt to improve the ejaculatory control (2 0000).*

Evidence

Both in clinical trials and in common clinical experience, the comorbidity between ED and premature ejaculation (PE) could be found in up to 50% of the patients with an ejaculatory dysfunction [150-154]. This is due to several pathophysiological reasons. In particular, Corona et al. [155] demonstrated in a recent meta-analysis that the presence of PE is associated with a significant increase in ED risk (OR: 3.68 [2.61;5.18]; $P < 0.0001$) and that patients with PE have lower IIEF-5 scores when compared to those without PE.

Remarks

It seems mandatory to check for the loss of control of erection and ejaculation in all patients with sexual dysfunction and in particular for those referred with PE, where the ED could be hidden and non-evident to the patient himself. Use

of psychometry, careful clinical history and discussing the issue with the partner may help with this complex diagnosis, addressing the management which should always start with the treatment of ED or subclinical ED (SED; see below)[156-159].

Partner sexual disorders and “couplepause”

Recommendation #29. *We recommend considering the partner and her/his sexual dysfunctions as direct or indirect risk factors for erectile dysfunction (Good Clinical Practice).*

Evidence

While it is well known that ED could be due to the relational risk factors mentioned above, scientific literature stressed with lower impact that the presence of a sexual dysfunction in the partner could amplify that of the patient. A typical mechanism has been described for the *couplepause*, where menopause and late onset hypogonadism (erroneously called *andropause*) can affect the sexual health of both the patient and partner [160]. Another representation is anorgasmia [161], severe dyspareunia or vaginismus [162], where impossible penetration frequently reduces the patient's self-esteem and self-confidence in his ability to obtain and maintain an erection. Similarly, it may also occur for impairments in the sexual desire [148, 163].

Remarks

A deep sexual diagnostic of the partner is highly advised, also by using dedicated psychometric tools [164]. We advocate for a new diagnostic (and therapeutic) paradigm that addresses the sexual health of the couple as a whole rather than treating the individual patient in isolation.

Sexual orientation

Recommendation #30. *We suggest non-judgmentally exploring patients' sexual orientation (and gender identity) and personal perceived attitudes towards it when managing their erectile dysfunction (2 ØØØØ).*

Evidence

It has been evidenced in non-heterosexual couples, that, in the same manner as for heterosexual couples, ED negatively impacts relationship quality. Furthermore, meta-analyzing available data, Barbonetti et al [165] found that non-heterosexual orientation is associated with 1.5-fold higher odds of reporting ED (OR = 1.49, 95% CI = 1.03-2.16; p = 0.04). Further research is needed in this field which still appears to be, unfortunately, in its infancy.

Remarks

Minority stress is an important risk factor for sexual problems in non-heterosexual cisgender men [166, 167]. Since internalized homophobia predicts poorer sexual quality of life in non-heterosexual men, [168, 169] this aspect should be carefully evaluated in the management of ED in patients with a non-heterosexual orientation.

Infertility

Recommendation #31. *We suggest investigating the presence of erectile dysfunction in the work up of couple infertility, particularly when undergoing assisted reproduction techniques (Good Clinical Practice).*

Evidence

The negative association between couple infertility and ED is well known [170, 171]. Among men of infertile couples, sexual dysfunctions including hypoactive sexual desire, ejaculation disorders and ED are frequent, ranging from 6.7% to 75% [170, 172]. ED rarely directly impairs male fertility, as in the case of absent or insufficient erection for penetration, leading to a reduced frequency of sexual intercourse [170]. In any case, the prevalence of ED is about one in six infertile men [170]. Moreover, it has been found that the prevalence of ED increases as a function of severity of semen quality impairment [173], and a survey of SIAMS reported ED in 56.2 % of men undergoing assisted reproduction techniques (ART) [174]. The relationship between male infertility and ED, particularly in men undergoing a complex diagnostic-therapeutic reproductive work-up, can be explained by the high psychological stress and the particular nature of the reproductive dysfunction, the characteristics of the diagnostic efforts and of the therapies [175]. Therefore, in the work-up of couple infertility, and particularly when undergoing ART, it might be useful to investigate the presence of ED and, in the event of a prevalent non-organic etiology, offer psychological counseling to improve the psychological health status and potentially the erectile function [102, 170]. For all these reasons, the *Inferto-Sex Syndrome* (ISS) has been recently defined as the sexual dysfunction in fertility care settings and during assisted

reproduction when the infertility (and its diagnosis and therapy) produces sexual dysfunction and the latter is causing the former[176].

Remarks

Only few studies investigated ED in infertile couples using validated tools [170]. In any case, infertility and its management are associated in men (and couples) with high psychological stress burdens, which, in turn, causes or predisposes them to ED [177, 178]. However, besides psychological stress, ED could also be a marker of hypogonadism and poor general health of infertile men [179].

DIAGNOSIS

The aim of the diagnosis of ED is to *i*) identify the severity of the symptom (subclinical, mild, moderate, severe), *ii*) identify the comorbidity with other sexual dysfunctions (e.g. hypoactive sexual disorder, ejaculatory disturbances), *iii*) find as many risk factors as possible ascertaining their impact on the single case of ED. Hence, the diagnosis is never aiming to exclude etiologies, but, on the contrary, to include the risk factors resulting from careful general and sexual anamnesis, focused physical examination, psychometric, laboratory, and instrumental tools evaluating their “specific weight” in the pathogenesis and care of ED.

Psychogenic vs. organic diagnosis of erectile dysfunction

Recommendation #32. *We recommend against the use of the redundant and stigmatizing term «psychogenic» for patients with non-organic, or idiopathic, erectile dysfunction. (Expert opinion).*

Recommendation #33. *We recommend against the “exclusion diagnosis”, as it is not evidence based, of erectile dysfunction. (Good clinical practice).*

Evidence

The term “psychogenic”- although still largely used in scientific literature, in textbooks and even in the guidelines - is overtly wrong for the reasons listed in the Table 2 [180]. When the full diagnostic effort does not produce evidence of organic risk factors, the term “non-organic” is strongly recommended instead of the obsolete and fallacious

“psychogenic”. Finally, note that the assumption that a gradual onset is typical of a physical cause, while a sudden onset demonstrates a psychogenic cause [181] is not only non-evidence based but also the source, without more robust evidence, of diagnostic and therapeutical mistakes.

Similarly, a number of texts suggest that when a physician has performed the major, if not all, instrumental diagnostic tools, she/he is authorized to diagnose a psychogenic ED (exclusion diagnosis)[182]. This illogical, non-evidence-based idea, quite unusual in other medical fields, harbors from Masters & Johnson, who claimed a >90% of psychogenic ED, in a time where radioimmunoassay of hormones and vascular diagnosis by doppler, just to mention some tools, were unknown[183]. Until robust and validated evidence is provided that all possible organic causes have been explored with all the possible diagnostic tools in a single patient - which is, by definition, impossible in medicine - the exclusion diagnosis is to be considered nonsense.

Remarks

A possible reason for the popularity of both the use of psychogenic and of the exclusion diagnosis, with the two mistakes strictly correlated, can be found in *i*) the simplicity and the apparently easiness of the concepts, unfortunately widespread also among patients: “if the doctor does not find a physical cause, it must be in the brain”; *ii*) the *argumentum ab auctoritate* (from Latin: argument from authority, where the opinion of an authority, such as Aristotle or, in our case, Masters & Johnson, is used as evidence to support an argument)[184];*iii*) the lack of education in sexual medicine and in psychosexology [185]; *iv*) the reciprocal advantages of some physicians and some psychologists to have medical or psychological patients in their offices.

Diagnosis of Subclinical Erectile Dysfunction

Recommendation #34. *We suggest considering subclinical erectile dysfunction as a taxonomic entity deserving clinical attention (Expert Opinion).*

Evidence

Some of the sexual dysfunctions, such as ED [8] and PE [159, 186] are defined based on evidence. Some others are not (yet), such as hypoactive sexual desire disorder, delayed ejaculation and anorgasmia. Although largely present in medicine, the term subclinical has only recently been considered, as in the case of “Subclinical ED” (SED)[187], the

pathological burden of men not affected by “clinical” ED [8] but experiencing a capricious and moody lack of erection or reduction of penile hardness. SED, as defined by strict major and minor criteria, has been recently observed in 4.4% of 11,200 patients attending an outpatient andrological center [188].

Remarks

Organic and psychological risk factors could both be present in this borderline condition, which is characterized by a psychosomatic-somatopsychic loop possibly leading, if untreated, to overt ED.

Self-reported questionnaires and structured interviews

Recommendation #35. *We suggest using validated questionnaires and structured interviews to support medical and sexological history during erectile dysfunction assessment and/or follow up (2000).*

Evidence

An accurate and detailed medical and sexological history represent crucial steps in the assessment of any patient and in particular for those seeking medical care for ED. In the latter case, cultural attitudes and social norms often restrain patients from consulting their physicians, thus delaying the diagnosis and understanding of the specific underlying factors [189]. When patients eventually consult, negative feelings such as anxiety and guiltiness can severely hamper the patient-physician relationship, preventing effective communication and empathy. Hence, validated and standardized case history tools, such as structured interviews and self-reported questionnaires, can allow clinicians to better investigate sexual health and diseases in ED patients [149]. Several sexual inventories are available analyzing different aspects of sexuality, such as erectile function, relationship and marital issues, intrapsychic impact, or the quality of life during the sexual symptoms and after recovery. The IIEF, especially in its abridged 5- or 6-item version of the original 15-item IIEF, is the most widely used tool to diagnose the presence and severity of ED and determine the efficacy of treatments in controlled clinical trials [149]. Conversely, the Structured Interview on Erectile Dysfunction (SIEDY) is the only validated structured interview which is able to simultaneously identify and quantify the pathogenetic domains present in ED subjects (i.e organic, marital and intrapsychic; [129, 141, 142]).

Remarks

Although available sexual inventories can allow the severity of sexual problems and specific underlying factors to be better investigated, demonstrating their utility in different clinical settings, they cannot be used as an evaluation in place of a full medical and sexual history, which remains a crucial step in ED patient evaluation [131].

Physical examination

Recommendation #36. *We recommend a focused genital-urinary and physical examination including penis, testis, and prostate evaluation, at least at the patient's first visit, in addition to the mandatory general physical examination (10000).*

Evidence

As reported above, a large body of evidence has documented that ED can be considered as a first sign of forthcoming CVD. [6]. Hence, an accurate general physical examination is mandatory in all patients seeking medical care for ED in order to rule out possible signs of CV problems such as peripheral murmurs or reduced peripheral pulses. Waist circumference evaluation more than body mass index calculation can suggest, when elevated, the concomitant presence of underlying metabolic problems [6]. Similarly, the palpation of an enlarged liver edge can underlie the presence of non-alcoholic fatty liver disease (NAFLD), which is closely associated with other metabolic problems, such as T2DM, as well as with organic ED [190, 191]. Finally, blood pressure measurement can reveal an undiagnosed arterial hypertension.

Besides a general physical, a specific andrological evaluation can obtain important information to support clinical diagnosis during ED patient evaluation. The detection of testicular and prostate mass necessitates ruling out the possible presence of cancers. On the other hand, the detection of low testicular volume, along with a reduced prostate volume, can support a diagnosis of male hypogonadism [54], which is more frequently of primary origin when bilateral gynecomastia is present [192]. Penis evaluation can allow for the discovery of concomitant penile abnormalities such as congenital curvature, or penile plaques suggestive of PD. In addition, the presence of hypospadias can support the diagnosis of congenital hypogonadism, when associated with other suggestive signs and symptoms (see above).

Remarks

We highly recommend that each physician dealing with patients seeking medical care for ED must perform an accurate general and andrological physical examination since they can obtain important specific information guiding and supporting the further diagnostic steps.

Metabolic and hormonal evaluation

Recommendation #37. *We recommend routine laboratory tests including: fasting glucose, glycated hemoglobin and triglycerides and total and HDL cholesterol, in all patients affected by erectile dysfunction (1 ØØØØ).*

Recommendation #38. *We recommend routine hormonal parameters including: LH, FSH, total testosterone, SHBG and albumin (for calculated free testosterone determination) in all patients affected by ED (1 ØØØØ).*

Recommendation #39. *We suggest considering prolactin and TSH evaluation in the presence of other sexual comorbidities such as reduced sexual desire or ejaculatory dysfunctions (2 ØØØØ).*

Evidence

Considering the frequent association among ED, DM (often undiagnosed) and CVD, all subjects complaining of ED should be checked for fasting plasma glucose (FPG), glycated hemoglobin (HbA1c) and lipid profile (LP)[102]. If FPG is >100 mg/dl, or HbA1c > 42 mmol/mol, further evaluations should be performed according to current guidelines (see https://snlg.iss.it/wp-content/uploads/2021/07/LG_379_diabete_2.pdf). LP should include total cholesterol, HDL-C and triglyceride plasma levels; LDL-C can be calculated by means of the Friedewald formula. If LDL-cholesterol is >130 mg/ dl, or 100 mg/dl in high CV risk subjects, further evaluation is needed (see below). Kidney and liver function tests and other biochemical assessments should be performed only if there are specific clinical indications.

T plays a crucial role in regulating male sexual function, acting at central and peripheral levels [78, 193]. Hence, T levels should be checked in all subjects with ED. Calculated free T has been suggested as a better marker of androgenization in patients with ED, considering that sex hormone binding globulin (SHBG) can profoundly influence total T levels in some clinical conditions, particularly in the presence of metabolic diseases [194]. Hence, the determination of SHBG is strongly suggested in all subjects in order to calculate free T. Total testosterone < 12 nmo/L and free T < 220 pmol/L should be considered as a cut-off for defining hypogonadism [194]. In addition, the concomitant determination of luteinizing hormone (LH) and follicular stimulating hormone (FSH) can help to define the

specific nature of the issue (primary or secondary hypogonadism). Specific diagnostic work-up and indications for management of hypogonadism have been reported elsewhere [194]

Other hormonal evaluations including PRL and thyroid stimulating hormone (TSH) should be performed only in the presence of specific symptoms, i.e. hypoactive sexual desire and ejaculatory dysfunction, since their association with ED is more conflicting (see above).

Remarks

We highly recommend that metabolic and T sampling should be performed in a fasting condition, collected in the early morning (between 8 and 11 AM) [54, 194-196].

Instrumental evaluation

Recommendation #40. *We suggest performing Penile Color Doppler Ultrasound, at least in flaccid condition, in all men with erectile dysfunction (20000).*

Recommendation #41. *We suggest performing Nocturnal Penile Tumescence and Rigidity (NPTR) test or other instrumental examinations only in selected patients (20000).*

Evidence

Penile Color Doppler Ultrasound (PCDU) associated with an injection of a vasoactive drug (dynamic PCDU) has been proposed, for a long time, as an instrumental diagnostic tool for measuring penile blood flow, and verifying penile vascular function, as well as penile structural abnormalities [197]. Although different vasoactive drugs have been used (or a combination of them), prostaglandin E1 (usually 10-20 µg) is the only one approved in Italy. Vascular response can be achieved between 5-30 minutes. The maximum response is defined as a peak systolic velocity (PSV) value above 25-35 cm/s, while end-diastolic velocity (EDV) value cutoff is <5 cm/s [197]. In addition, penile tumescence and rigidity can be described using objective parameters in a four-point scale: 1= no response; 2= rigidity, insufficient for intercourse (< 50%); 3= rigidity, sufficient for intercourse (> 50%); 4= full erection (>90%), as previously described [198]. A large body of evidence has documented that impaired dynamic PSV after PGE1 stimulation can be considered a marker of systemic vascular damage and an early sign of forthcoming MACE [6]. Interestingly, the latter is particularly valid in younger patients with unidentified CV risk factors, whereas in older subjects the predicting role of

PCDU is attenuated by the presence of comorbidities [102, 199, 200]. Although PCDU with vasoactive drug injection is widely employed as an initial diagnostic tool during the workup of ED, it is regarded as cumbersome, time-consuming, and especially operator-dependent [197]. Therefore, the use of penile peak systolic velocity and penile acceleration (FPA) evaluation in the flaccid (without PGE1 stimulation) condition have been proposed as alternative predictive parameters of CV risk [199, 200].

Nocturnal Penile Tumescence and Rigidity (NPTR, Rigiscan) assesses the natural erection that happens during night sleeping and early awakening, because it is associated with the rapid eye movement pattern of sleep [201]. Normal values include at least one episode of rigidity >70% lasting >10 minutes at tip during 3 nights of evaluation [201]. Although it has historically been employed for diagnosing the non-organic causes of ED, its contemporary use is limited due to high cost and possible confounding factors, including sleep quality and technical difficulties [201, 202].

The use of several other investigations – such as Neuro-Physiological Testing (NPT), Dynamic Infusion Cavrosometry and Cavrosography (DICC), Computed Tomography Angiography (CTA), selective Penile Angiography (PA) and Magnetic Resonance Arteriography (MRN)– is limited to specific evaluations of ED [102]. In particular, while NPT can be useful when suspecting a neurological cause of ED, DICC, CTA, PA and MRN can be used in the suspicion of congenital or acquired vascular abnormalities, such as after a trauma or before surgery [102].

Remarks

The specific cut-off value for dynamic PSV at PCDU able to identify patients at high risk for CVD is still an object of intense debate. There is, however, an overall agreement that dynamic PSV >35 cm/sec can exclude a vascular problem, whereas dynamic PSV < 25 cm/sec is highly suspected for a vascular insufficiency. There is a gray zone between 25-35 cm/sec which identifies subjects at high risk [102]. Although PSV < 13 mc/sec [203] and acceleration < 1.17 cm/sec² [199] evaluated in flaccid conditions have been proposed as alternative parameters for the diagnosis of penile vascular flow impairment, their role in clinical practice needs further validation.

Cardiological assessment

Recommendation #42. *We suggest that coronary artery calcium score (if permitted by local expertise and availability), could be considered as a further diagnostic test in men with calculated risks around decision thresholds (low-to-intermediate CVD risk profile), in order to relocate them to different risk groups (20000).*

Evidence

According to the III Princeton Consensus Panel, ED patients can be classified as low-indeterminate or high CV risk depending on the presence of associated CV risk factors [204]. Further cardiological evaluation is required for subjects classified in the indeterminate-risk before any further therapeutic work-up [204]. It is the opinion of the present Panel that SCORE-2 and SCORE-2 OP algorithms [39] represent the best instruments to stratify CV risk even in ED subjects. Coronary artery calcium (CAC) scoring Coronary Tomography scan has demonstrated clinical usefulness in the stratification of CV risk in addition to conventional CV risk factors, and should be considered as a further diagnostic test in men with calculated risks around decision thresholds (low-to-intermediate CVD risk profile), in order to relocate them to different risk groups also if not supported by evidence [39]. However, its widespread use should be carefully considered according to local expertise, availability, and cost-effectiveness [39]. Exercise stress ECG has an inferior diagnostic performance, when compared to stress diagnostic imaging tests, and it presents important limitations when obstructive CAD is present [40]. In addition, exercise stress ECG cannot be used as diagnostic tool for CAD in subjects with ECG abnormalities that prevent interpretation of the ST-segment changes during stress (i.e. left bundle branch block (LBBB), paced rhythm, Wolff-Parkinson-White syndrome, >0.1 mV ST-segment depression on resting ECG, or who are being treated with digitalis) [40]. When CAC is not available, carotid ultrasound should be considered as an alternative diagnostic tool, especially in the presence of plaque (i.e. focal wall thickening $>50\%$ greater than the surrounding vessel wall, or as a focal region with an intima-media thickness (IMT) measurement >1.5 mm that protrudes into the lumen) [39]. Finally, available evidence suggests that PCDU parameters evaluated either in flaccid or dynamic conditions can provide further insights, especially in low-risk patients contributing to the stratification of CV in ED patients [6].

Remarks

Is important to recognize that when population-based studies are considered, the majority of CV events occur in subjects classified as at “lower-CV risk” [6, 205]. Hence, identifying new parameters contributing to this “residual CV risk” represents a challenge for the near future. It is the opinion of the present Panel that SCORE-2 and SCORE-2 OP represent the best instruments to classify CV risk even in ED subjects. The presence of arteriogenic ED as detected by PCDU should be considered a further parameter to be taken into account supporting a high CV risk profile. Finally, it should be emphasized that, independently of the calculated CV risk profile, lifestyle changes and the optimization of associated morbidities represent the major cornerstone for all people, as well as for those consulting for ED. The

therapeutical targets related to the concomitant risk factors must be based on the CV risk stratification, as more conservative thresholds are required in patients with higher CV risk [39].

Psychological assessment

Recommendation #43. *We suggest educational, psychological, psycho-sexological and marital assessment in all patients with ED (Good clinical practice).*

Evidence and remarks

A common mistake is to consider psychological assessment only in selected patients, such as those with (apparently) non-organic ED [180]. Considering that all sexual dysfunction, irrespectively of the cause, is *bona fide* to be considered able to produce (as well to be produced by) a psychological derangement with both intrapsychic and/or relational components [140, 142, 206, 207], it is nonsense to limit the psychological evaluation to selected patients. Despite the advice of classical psycho-sexology to consider the couple as the real patient in addressing sexual symptoms [183], less logical evidence could support the universal need to involve the partner(s) in the diagnosis and in the management of ED. This is due to two reasons: *i*) the single population is currently increasing in western societies. A couple-based sexology may be inadequate; *ii*) several male patients (in the case of ED, but also in other sexual dysfunctions) dislike sharing with partners either the visit with the sexual physician or psycho-sexologists as well as their therapeutical choices.

Psychiatric assessment

Recommendation #44. *We recommend investigating anxiety and depressive symptoms, through standardized self-reported assessment, in men with erectile dysfunction, due to high incidences of these disorders (1 0000).*

Recommendation #45. *We suggest using as screening tools “General Anxiety Disorder-7” and “Patient Health Questionnaire-9”, for anxiety and depression, respectively (20000).*

Evidence

The use of self-reported scales can identify the presence of anxiety or depressive disorders with a good level of reliability. General Anxiety Disorder-7 (GAD-7) [208] and Patient Health Questionnaire-9 (PHQ-9)[209], two of the most used tests to measure, respectively, anxiety and depression symptomatology, are appreciated because of their fast execution. In men with ED, GAD-7 and PHQ-9 were useful in detecting the presence of anxiety and depressive illness as well [210]. Alternatively, the Middlesex Hospital Questionnaire (MHQ) [211] has been successfully applied in a large series of patients seeking medical care for ED [43, 132].

Remarks

The use of self-reported assessment instruments of anxiety and depression should be indicated at the first clinical evaluation of patients with ED. Because of the high comorbidity between anxiety and depression, instruments covering both conditions should be proposed to patients with ED. In a non-specialist context for mental health care, the use of a reliable self-reported assessment for anxiety and depression can identify those patients with ED to whom specific treatments for anxiety and depressive disorders should be addressed along with following the evolution of these illnesses.

THERAPY

Etiological (or causal) therapies

All the therapies directly addressing the causes or that act as risk factors of ED are to be considered etiological. Therapies addressing lifestyle (diet, smoking cessation, physical activity, etc.), and hormonal therapies for endocrine diseases, are to be considered typical etiological therapies. Etiological therapies may be sufficient in curing ED or they may need the support of a symptomatic therapy (see below [156])

Diet

Recommendation #46. *We recommend the assumption of healthy diets to reduce the risk of ED (10000).*

Recommendation #47. *We recommend the use of Mediterranean dietary pattern to prevent the development or reduce the progression of ED in men with diabetes, obesity or metabolic syndrome (10000).*

Evidence

A dietary pattern which is high in fruit, vegetables, nuts, whole grains, and fish but low in red and processed meat and refined grains is more represented in subjects without ED [212]. There is evidence from several cross-sectional studies that healthy diets characterized by high content in vegetables, fruit, mono-unsaturated fats and flavonoids are associated with a low prevalence of ED in both general and clinical populations [212, 213]. Moreover, large prospective cohort studies found an inverse association between Mediterranean diet or healthy dietary patterns with a high content of flavonoid-rich food and the incidence of ED [212, 213]. RCTs involving men with obesity, metabolic syndrome or DM showed a favorable effect of the Mediterranean dietary pattern on erectile function [212, 213]. In the first trial specifically designed to test the effects of intensive lifestyle changes, including advice on Mediterranean diet to obtain weight loss in 55 obese men with ED, a significant improvement of IIEF score was observed after 2 years of significant weight loss, as compared with matched-control obese with ED who received general information about healthy food choices and exercise [214]. In another RCT [215], men with metabolic syndrome and ED assigned to the Mediterranean diet improved their erectile function, measured by an increase of IIEF-5 scores after 2 years. Additionally, more men with ED at baseline regained erectile function compared with controls (37% vs 7%; $p = 0.015$). In a secondary analysis of the MEditerraneanDiet and Type 2 diAbetes (MÉDITA) trial, men with T2DM randomized to a Mediterranean diet showed a 56% relative risk reduction in incident ED, a lesser decrease in IIEF (1.22, $p = 0.024$), and a modest albeit significant improvement of weight, HbA1c, systolic blood pressure and C-reactive protein, as compared with men assigned to a low-fat diet [216].

Remarks

The specific mechanism through which a Mediterranean diet can improve ED as compared to other weight loss regimens is not completely understood. The distinctive characteristics of the Mediterranean diet are the large consumption of plant-based food, with olive oil as the main source of fat and low to moderate consumption of wine with meals. In this scenario, working mechanisms by which a Mediterranean diet can improve ED in men with metabolic disorders include amelioration of endothelial dysfunction, insulin-resistance, and the low-grade inflammatory state associated with metabolic diseases [216]. Interestingly an anti-inflammatory state is also one of the main advantages of a very-low calorie ketogenic diet [217]. Preliminary data suggest positive outcomes on sexual function which should be confirmed in larger studies [213].

Physical exercise

Recommendation #48. *We recommend physical activity in all subjects with ED particularly in overweight or obese subjects. (10000).*

Evidence and remarks

A sedentary lifestyle doubles the risk of having ED, whereas physical activity (PA) has been identified as the strongest lifestyle factor associated with improved erectile function [52]. Evidence suggests that the leading mechanisms through which PA improves ED is weight loss and increased endothelial nitric oxide production [52]. As shown in a RCT [49] the implementation of PA in men with ED ameliorates endothelial dysfunction and vascular inflammation, thus resulting in a 4.0-point improvement of the IIEF-5 score. PA should consist of at least 40 minutes of aerobic exercise of moderate to vigorous intensity, 4 times per week, under supervised training [102]. However, the specific comparisons among different PA regimens to improve ED are still lacking.

Bariatric surgery

Recommendation #49. *We suggest bariatric surgery to decrease erectile dysfunction in morbidly obese men (20000).*

Evidence

Numerous strands of research have demonstrated that surgery-induced weight loss is correlated with higher T levels as compared to the increase obtained by lifestyle interventions only, suggesting a potential therapeutic role of surgery for the treatment of hypogonadism in obese males [218]. Otherwise, the effects of bariatric surgery on ED and fertility are still controversial [56, 219-221]. A prospective cohort study of 32 men undergoing Roux-en-Y gastric bypass reported significant increases in total T, but non-significant improvements in sexual functioning, four years post operation [222]. Moreover, several case reports demonstrated that bariatric surgery may affect fertility [221]. In contrast, two different systematic reviews and meta-analyses reported that bariatric surgery led to a significant increase in IIEF-total score and erectile function score, but did not improve orgasmic function [56, 223].

Smoking and drug cessation

Recommendation #50. *We recommend quitting smoke as a major therapeutical strategy to improve general and sexual health and erectile function (100000).*

Recommendation #51. *We recommend quitting abuse of alcohol and illegal psychotropic substances as major therapeutical strategies to improve general and sexual health, including erectile function (100000).*

Recommendation #52. *We suggest discussing with the physician the prescription of drugs with the lowest impact on sexual function (200000).*

Evidence and remarks

Smoking tobacco has been robustly and definitively demonstrated as a major cause of NCDs, but it is also negatively associated with ED and impaired sperm parameters [224]. The MMAS reported that cigarette smoking doubles the risk of developing ED [225, 226], while a systematic review shows a difference of 12.4% in the proportion of smokers between ED men (40.1%) and the general population (27.7%) [227]. Other meta-analyses support that current smoking behavior is associated with ED in a dose-dependent and duration manner and that the past use of cigarettes increased the risk of ED when compared to never smoking [228]. A number of patients addicted to tobacco smoke appear unable to quit nicotine for a number of reasons. It is matter of discussion whether electronic products, such as electronic cigarettes (e-Cig) and heat-not-burn (HnB) devices, may reduce the impact of tar on general health [229]. In fact, the real impact of these devices on erectile function remains to be empirically determined [230]. It is to be noted that American cardiologists openly consider e-Cig and HnB devices as tools to reduce the CV risk in patients refractory to the fundamental, healthy choice to definitively quit smoking [229]. Robust evidence is need to advise the same in ED patients.

Finally, quitting the abuse of alcohol [231] and the use of illegal psychotropic drugs [232], after a convenient period of recovery, or shifting from legal drugs increasing the risk of ED to similar medical treatments with a lower impact on sexuality [233, 234], are to be expected as favoring the erectile function and should precede or accompany any symptomatic treatment.

Hypogonadism

Recommendation #53. *We recommend treating hypogonadal ED patients with testosterone, with the best results obtained in patients with an overt hypogonadism (i.e. total T <8 nmol/L) (1 0000).*

Evidence

As reported above, sexual dysfunction, including ED, is the most genuine symptom of hypogonadism in middle aged and older European men [235]. In virtually all the published meta-analyses, TRT improved erectile function, although with different effect size [236, 237]. In particular, in a meta-analysis, with the main outcome measure the IIEF-EFD, T demonstrated a 2-3 point IIEF-EFD increase [238]. This effect was modulated positively by the severity of hypogonadism and negatively by the presence of comorbidities, such as diabetes or obesity [238]. It is interesting to note that this positive effect is definitively lower than the one obtained with any PDE5 inhibitor (at least 5 points IIEF-EFD).

Remarks

The aforementioned, relatively mild, positive effects of T on erectile function was not apparent in RCTs enrolling eugonadal or mixed populations, suggesting that this therapy is useful only in hypogonadal patients [193, 239]. The specific role of TRT in improving the responsiveness to PDE5i in hypogonadal men is still conflicting and must be confirmed in larger trials [237].

Other associated endocrine diseases

Recommendation #54. *We recommend treating ED patients with severe hyperprolactinemia to improve sexual desire, testosterone levels and erectile function (10000).*

Recommendation #55. *We suggest treating patients with hypo-hyperthyroidism (20000) or hypocortisolism (20000) with their specific therapy to also improve ED.*

Evidence

Although hyperprolactinemia represents quite a rare cause of ED, severe hyperprolactinemia (> 35 ng/ml) is quite often associated with ED and reduced libido, independently from the cause of the problem [84]. Conversely, the presence of lower levels of PRL should be better investigated in order to exclude functional forms, due to venipuncture effect or false conditions, such as in the case of macroprolactinemia [84]. When the problem is related to the concomitant use of drugs increasing PRL levels, the condition can be managed with the withdrawal of the responsible treatment, when possible [240]. In all other cases, and especially for prolactinomas, dopamine agonists (bromocriptine and cabergoline) are the recommended choice. Cabergoline, considering its longer half-life, represents a more manageable drug when compared to bromocriptine, because it often results in better outcomes considering either erectile or orgasmic function [241]. Normalization of PRL levels is usually associated with an improvement of sexual function and T levels. If T levels are not normalized by dopamine agonists, T supplementation could be added [84, 242].

As reported above, the role of other hormones in the regulation of male sexual function is still conflicting. Limited evidence indicates that normalization of thyroid hormones in the presence of hypo- and, more frequently, hyperthyroidism can result in the improvement of male sexual function and ED [84, 87, 90]. Similarly, data have been reported after the normalization of serum cortisol in subjects with Addison's disease [243].

Remarks

ED has been also frequently reported as a possible consequence of acromegaly and Cushing's syndrome [91, 244]. However, in the latter cases, the problem seems to be related to the vascular complications associated with growth hormone or cortisol excess rather than to a direct effect of the hormone imbalance.

Psychoanalysis

Recommendation #56. *We suggest considering psychoanalysis as a therapeutical option in selected patients in whom other therapeutic approaches for erectile dysfunction have failed (Expert opinion).*

Evidence and remarks

Clinical trials implementing individual or group therapy based on the psychoanalytical model for the treatment of ED are lacking. In fact, evidence for the use of a psychoanalytic approach in the treatment of ED is only supported by anecdotal reports [245]. Sigmund Freud's psychoanalysis has established numerous notions and hypotheses that are still relevant to contemporary sexual medicine. ED, or “psychic impotence”, was explained by Freud as due to some characteristics in the sexual partner because ED emerged in men during intercourse with particular partners (situational ED). Freud’s pioneering work has, however, progressively revealed lacking practical relevance to treating ED. The only exceptions are those clinical circumstances in which a psychoanalytic approach to analyze psychic conflicts, potentially underlying ED, may be indicated for patients with an ED “resistant-to-treatment” condition (i.e., unresponsive to pharmacological treatments or behavioral sex therapy for ED) [245]. It cannot be excluded, however, that neurotic traits or personalities may obtain general psychological advantages from psychoanalysis which may indirectly produce sexual benefits. Empirical studies are needed to confirm this hypothesis.

SYMPTOMATIC THERAPIES

The symptomatic therapies of ED are those addressing the symptom, i.e. the chronic (clinical) or partial (subclinical) inability to obtain and/or maintain an erection, irrespectively of the etiological or risk factor related to the sexual dysfunction. Note that, among a number of medical and surgical therapies, cognitive-behavioral and sexual therapies are to be considered symptomatic in nature. Typically, relapses are not rare after withdrawal from all these therapies. However, if the symptomatic therapies are supported by counseling and found successful and satisfactory by the patients and their partners, the possibility of producing a “positive memory” instead of a “prevision of failure” would increase the likelihood of a full recovery and, in some patients, a complete sexual rehabilitation.

Pharmacological Therapies

Pharmacological therapies, such as Phosphodiesterase type 5 inhibitors (PDE5i), are to be considered the gold therapeutic standard after (which is the best choice) or together (with a motivational aim) with the lifestyle changes affecting erectile function. When the cause of ED is known, it appears also clinically sound to prescribe PDE5i after failure of the corresponding etiological treatment (e.g. hypogonadism).

Oral therapy

Recommendation #57. *We recommend using short- or long-acting PDE5i as first-line therapy for the treatment of ED (10000).*

Recommendation #58. *We suggest preferring short-acting PDE5i in patients with high CV risk (2 0000).*

Recommendation #59. *We recommend preferring long-acting PDE5i in patients with LUTS (10000).*

Recommendation #60. *We suggest combination of chronic and on demand PDE5i in patients not responding to conventional therapy (Expert Opinion).*

Recommendation #61. *We recommend against the use of counterfeit PDE5i (Good clinical practice).*

Evidence

PDE5i are a well recognized first-line therapy for ED patients. They increase NO signaling by inhibiting the degradation of its downstream effector, cGMP, working as “inhibitors of inhibition”, i.e. the PDE5, the enzyme providing the breakdown of cGMP and thus blocking the smooth muscle cell relaxation in the corpora cavernosa [246]. In the majority of European markets, four different PDE5i are currently available: sildenafil, tadalafil, vardenafil, and avanafil. These molecules differ in their pharmacokinetic and pharmacodynamics characteristics as reported in Table 3. All molecules show a rather rapid onset of action, within 30 minutes after oral administration [36, 102, 247]. Sildenafil, vardenafil and avanafil have only a limited oral bioactivity (about 40%, 10% and 15%, respectively) due to an important pre-systemic metabolism through CYP3A4 and/or CYP3A5 pathways [36, 102, 247]. Tadalafil is the PDE5i with the longest mean half-life (17.5 hours), when compared to the others, but with the longest time-to-onset, corresponding to the longest T_{max} (Table 3). A high-fat meal (about 910 Kcal, 57% of which from fat) can reduce the absorption of sildenafil and vardenafil, possibly delaying the onset of action, but has no effect on tadalafil pharmacokinetics (Table 3). All products are available in tablet formulations. In addition, sildenafil and vardenafil are also available in practical orodispersible formulations [248]. Finally, more recently sildenafil oral film (ODF) has been marketed in several countries, including Italy [249]. The ODF does not require either water or swallowing, thus enhancing compliance. [250]. In addition to the benefit of all orodispersible formulations, in that they reduce first-pass metabolism, an enhanced bioavailability and a decreased incidence of side-effects may also be possible [249]. Moreover, the ODF formulation respects the need for privacy felt to be essential by several patients for a perfect compliance with the ED oral treatments [251].

All PDE5i are metabolized mainly via the CYP3A4 pathway (Table 3). Moreover, CYP2C9, CYP2C19 and CYP2D6 contribute to sildenafil and avanafil metabolism while CYP2C9 is also involved in vardenafil metabolism [36, 102, 247]. Hence the concomitant use of drugs interfering with the latter CYP metabolism should be adequately managed (see supplementary Table 1). Similarly, the concomitant use of nitrates is contraindicated for all PDE5i and precaution should be considered in patients taking alpha-blockers.

Moreover, it should be considered that a dosage adjustment is required for sildenafil, vardenafil and tadalafil in cases of severe renal impairment (estimated glomerular filtration rate < 30 ml/min), whereas avanafil is contraindicated, due to the lack of available studies. In addition, the presence of a severe liver impairment (Child-Pugh class 3) requires dose adjustment for sildenafil and vardenafil and it is a contraindication for the use of avanafil. No dosage modification is suggested for tadalafil [36, 102, 247].

The adverse events are limited and mainly related to the interaction with other PDE isoforms (Table 4)[252-255]. Although one-to-one comparisons are lacking, a meta-analysis related to placebo-controlled RCTs, based on the use of tablets, showed a similar clinical efficacy among all available PDE5i [256]. The same meta-analysis showed that the lowest overall rate of all adverse events was reported with avanafil [256]. CV safety of all PDE5i is high and possible CV positive effects have even been documented with the use of this family of drugs [102], with a PCDU measured superiority of sildenafil at the highest doses [257]. However, in order to avoid negative outcomes with the use of concomitant medication, in the presence of recurrence of an acute event, short-acting PDE5i should be preferred in patients with high CV risk [204]. On the other hand, it should be recognized that only a long-acting tadalafil has been approved as daily therapy for the treatment of LUTS [102].

Finally, PDE5i is the most counterfeited medication with potentially large harmful effects on unaware consumers. Patients, sexologists, pharmacists, physicians, and healthcare authorities should collaborate to find educational strategies to face this risky and widespread phenomenon. [251]. Addressing this topic when counseling the patient with ED should be considered of pivotal importance.

Remarks

Despite their clinical efficacy and safety profile, the PDE5i-associated dropout is still quite high, up to 50% in one year [256]. A combination of wrong expectations, incorrect information, presence of comorbidities, as well as marital and intrapsychic factors can independently play a role in the latter phenomenon [189, 258]. Hence, physicians dealing with subjects seeking medical care for ED should be aware that an adequately tailored therapy should be based on adequate

counseling, which is the cornerstone for the success of any sexual treatment. Lifestyle modification and the optimization of comorbidities must be part of the therapeutic strategy. The presence of hypogonadism must be corrected before a PDE5i prescription.

Combined therapy with other drugs, such as PGE1, vacuum devices or low-intensity shockwave therapy, still represents a challenge due to the lack of controlled studies. However, limited data suggest that the combination of tadalafil daily dosing with a short-acting PDE5i can improve outcomes, without a significant increase in side-effects [259, 260]. Table 5 may help in the choice of PDE5i [156, 261-270]

Finally, the SIAMS and the scientific societies involved in these guidelines are not against, in principle, a non-prescription, over-the-counter (OTC) regimen for low and intermediate dosages of PDE5i instead of the current prescription (Rx) regimen [251]. In fact, in some European countries, sildenafil 50 mg has been available OTC since 2018. An early, multi-center, pharmacy-based selection study has shown that the proposed OTC model could ensure a high degree of accuracy and specificity in the patient and pharmacist decision-making [271]. This strategy would decrease the risk of the black market of PDE5i as well as the barriers to seeking treatment for ED [189, 258, 272].

Topical therapy

Recommendation #62. *We suggest topical or intraurethral alprostadil in men with erectile dysfunction in whom type 5 phosphodiesterase inhibitors are contraindicated or not tolerated or not effective and who prefer a less-invasive treatment (2 ØØØØ).*

Evidence

Topical or intraurethral alprostadil is an effective, safe, approved and currently available treatment for ED [102, 273]. Alprostadil is a synthetic analog of PGE1, which activates the cyclic adenosine monophosphate (cAMP) pathway in cavernous smooth muscle cells, inducing vasodilatation and erection. It can be administered in urethral meatus using a topical cream formulation (alprostadil 300 µg added to a permeation chemical enhancer to facilitate its absorption) or by the intra-urethral insertion of a medicated pellet (at a recommended starting dose of 500 µg, that can be increased to 1000 µg) [102, 273]. Both topical and intraurethral alprostadil are significantly more effective than placebo in improving erectile function in men with mild-to-severe ED, although their efficacy is significantly lower when compared to that of PDE5i or intracavernous alprostadil injection (see below) [102, 273]. The effect of this treatment is reached in

approximately 10-12 minutes and lasts longer than one hour, with a satisfactory erectile response of 73-83% [102, 273]. Topical or intraurethral alprostadil do not interfere with other drugs and have no specific contraindications, while adverse effects are almost exclusively local [102, 273].

Remarks

There is no evidence of different efficacy between the topical or intraurethral formulations, but a recent trial observed that, compared to the standard administration, the intra-meatal application of alprostadil cream could be more effective [274]. The usefulness of topical or intraurethral alprostadil could be precluded by penile abnormalities and should be excluded in men with balanitis or vascular states prone to thrombosis [102, 273].

Intracavernosal injection (ICI) of vasoactive substances

Recommendation #63. *We recommend intracavernosal therapy with alprostadil in men with erectile dysfunction in whom PDE5i are contraindicated or not tolerated or not effective due to organic reasons (1 0000).*

Evidence

In Italy and in many other countries, alprostadil (PGE1) is the only drug approved for intracavernous (ICI) treatment of ED. Available data have shown that alprostadil is effective at a dosage of 5-20 µg in 70-87% of cases in a dose-dependent manner [275]. Adverse events are usually locally limited and include penile pain (1-11%), fibrosis (5-7%), bleeding and ecchymosis (7-8%), whereas the occurrence of priapism is quite rare (1-2%) [102, 275]. ICI with alprostadil should be avoided in patients with known hypersensitivity to alprostadil and in those with a predisposition to priapism (e.g. sickle cell anemia, multiple myeloma and leukemia). Conversely, the concomitant use of anticoagulant medications does not represent an absolute contraindication [275].

Remarks

The combination of ICI of PGE1 with other drugs such as papaverine (8-16 mg) and phentolamine (0.2-0.4 mg), also known as trimix, has been frequently used to improve PGE1 efficacy rates. However, it is important to recognize that the latter approach has never been licensed for ED [102].

Physical therapies

In patients not responsive to any pharmacological treatment, or when medications are contraindicated, according to their preferences, mechanical therapies, such as vacuum devices, prosthesis surgery, and shockwaves (discussed in another section of these Guidelines) can be prescribed. Furthermore, other newer therapies are expected in the future.

Devices

Recommendation #64. *We suggest considering vacuum erection devices alone or as a combined therapy in men with erectile dysfunction in whom PDE5i and intracavernosal/transurethral therapies are contraindicated or not tolerated or not effective (2 ØØØØ).*

Evidence

Vacuum erection devices (VED) include a wide variety of instruments based on a closed-end cylinder, vacuum pump, and a constriction ring. The vacuum chamber generates a negative pressure allowing for a passive enlargement of the corpora cavernosa, which together with a constrictor ring placed at the base of the penis to retain blood within the corpora, cause an erection to be reached. Available data indicate a very high success rate (70-90%) regardless of ED etiology and type of population considered [102, 276]. However, long-term data indicate a very high dropout rate (up to 65%) which partially mitigates the excellent reported outcomes [102, 256].

Remarks

The vast majority of the available data on VED were published before PDE5i market availability. Accordingly, the use of VED has shown a reasonably strong reduction after the release of PDE5i on the market. Nevertheless, VED can still represent an important therapeutic option especially in combination with other drugs, such as PDE5i or ICI, to improve outcomes or during penile rehabilitation after pelvic surgery or radical prostatectomy [276]. Similarly, VED can be considered a valid option to PDE5i or PGE1, when specific contraindications are present [276].

Surgical Therapy

Recommendation #65. *We recommend using penile prosthesis implantations in men with erectile dysfunction in whom all other therapies are not effective or contraindicated (1ØØØØ).*

Evidence

Penile prosthesis implantation (PPI) is a definitive treatment for ED that should be offered to all subjects who do not respond to less invasive therapies or who have specific contraindications to them [102, 277]. Patients with ED and PD, requiring surgical management, benefit from early placement of penile prosthesis [102, 277]. Patients should be informed of the increased risk of complications if they are actively smoking or affected either by obesity or other uncontrolled comorbidities, such as DM [102, 277]. Among commercial prostheses, inflatable penile prostheses (particularly 3-piece) with an infection-retardant coating have a lower infection rate and a higher couples' satisfaction than malleable penile prosthesis [102, 277]. Specific surgical procedures for PPI is beyond the aim of the present consensus and have been revised elsewhere [102, 277]. When the patients are correctly selected before the surgical approach, PPI is associated with very high satisfaction rates among both patients and partners (around 90-100%) [277].

Remarks

It is important to recognize that most of the studies carried out so far comparing PPI outcomes and long-term follow-up are observational and, often, retrospective. Therefore, higher quality data from RCTs and multi-center studies with long-term follow-up are needed before definitive results can be drawn. Other surgical vascular interventions including penile revascularization surgery for arterial insufficiency and penile venous surgery for corpora veno-occlusive dysfunction, remain debatable and unproven, and indicated only in selected cases [278].

Finally, a careful psycho-sexological evaluation and counseling must proceed PPI, also to avoid risks (e.g. sexual offenders) or unrealistic expectations. However, more research is needed to develop and validate a specific, complete and easy-to-use questionnaire for patients undergoing this particular surgery.

Counseling and psychotherapies

Recommendation #66. *We suggest integrating psycho-sexological therapies with lifestyle changes, medical, physical, and surgical therapies (2 ØØØØ).*

Recommendation #67. *We recommend cognitive-behavioral approaches as the gold psychotherapeutic standard (1ØØØØ).*

Evidence

While counseling is a duty of the physician, the surgeon, and the pharmacist, psychotherapies are performed by licensed psychotherapists, possibly with specific experience and well-trained skills in human sexual behavior and related dysfunctions. Several reports demonstrated that, despite the proven efficacy, the relative safety, and a cost considered not excessive by the majority of the patients, the high dropout rate of PDE5i is mainly due to unrealistic expectations of the user, which are proportional to the lack of counseling from the doctor [258]. A holistic approach which considers the biological, psychological and relational aspects is the advised treatment for ED. Integrated medical and psycho-sexological therapy requires a mutual understanding of, and respect for, the different disciplines involved in the management of all sexual dysfunctions [270, 279-281]. Cognitive behavioral therapy (CBT) was found to be an effective treatment strategy for non-organic ED, or even organic ED with important cognitive and behavioral comorbidities or a non-organic nature [146, 282, 283].

Remarks

A common mistake is to limit CBT to patients who, after (apparently) proper medical investigations, are diagnosed as affected by non-organic ED [284]. On the contrary, in real-life clinical practice, intrapsychic and/or relational involvements are seen, if carefully searched for, in virtually all patients with ED. Although expensive, time-consuming, culture-sensitive, and dramatically operator-dependent, CBT should be considered as a robust help in reaching sexual health when a medical remedy is prescribed.

CONTROVERSIAL ISSUES/FUTURE DIRECTIONS

The last part of these Guidelines is a testimony to the fact that the field of sexual medicine in general, and that of ED in particular, is growing and continuously changing its landscape. Moreover, it appears clear that it must be fed and watered with more research and robust evidence, which are currently not enough in the topics here discussed.

Hemodynamic procedures and Regeneration therapy

Recommendation #68. *Due to limited available data, no clear recommendations on the use of stem cells or platelet-rich plasma as well as on penile mechanical hemodynamic revascularization procedure can be provided.*

Evidence

Multi-potential stem cells (SCs) have showed promising therapeutic outcomes in several degenerative and vascular diseases [285]. A recent meta-analysis, considering data derived from rats, has shown that adipose derived SCs (ADSCs) can allow erectile function to be recovered and cavernous structures regenerated by significantly increased neuronal NO synthase(nNOS), cavernous smooth muscle content, the ratio of cavernous smooth muscle and collagen and cGMP.

However, data on humans are still limited and only preliminary results are available [286]. Platelet-rich plasma (PRP) is based on highly concentrated platelets and plasma proteins derived from the centrifugation of whole blood. A large body of evidence has clarified that platelets can release a wide range of biologically active substances including growth factors, chemokines and cytokines which can enhance immunological responses and help in maintaining and modulating inflammation[287]. Along with an artificial activator, including thrombin or calcium chloride, PRP can be used for wound healing and proper tissue regeneration. Preclinical data suggest a positive effect of PRP in animal models of cavernous nerve injury and vasculogenic ED, however data on humans are too limited to draw any conclusions [288].

Remarks

Emerging evidence provides data supporting a possible role of percutaneous approach with drug eluting balloon and oral drug eluting stent implantation [289, 290]. However long-term data and high-quality studies are lacking. Hence larger studies are advisable to better clarify these preliminary results [289, 290].

Shockwave

Recommendation #69. *We suggest considering low intensity shockwave therapy in patients with mild vasculogenic ED not responding to PDE5i (20000).*

Evidence

Low-intensity shockwave therapy (LI-SWT) is a physical treatment based on acoustic waves creating an alternation of positive pressure, which is referred to as a 'shock', followed by a longer-lasting period of negative pressure. This

approach has been successfully applied for the treatment of chronic wound and musculoskeletal diseases since a long time. Basically, mechanical stimulation can increase smooth muscle and endothelial content due to up-regulation of angiogenic factors stimulated by “shear stress”. In addition, a recruitment of endogenous mesenchymal stem-cells and stimulation of endothelium regeneration, nNOS positive nerves and smooth muscle tissue have been also described. Finally a possible nerve regeneration by enhancing the recruitment and the activation of progenitor Schwann cells has been suggested [29]. Increasing evidence derived from both RCTs and observational studies advocated a possible role of LI-SWT in subjects with mild vasculogenic ED and, in particular, in those not responding to PDE5i [102, 107]. Available studies showed that LI-SWT can significantly increase the patient derived outcomes including IIEF and Erection Hardness Score when compared to placebo, however, the improvement appears to be modest and improved penile hemodynamics, as well as long-term efficacy, are uncertain [107].

Remarks

The main problems related to the use of LI-SWT is related to the relatively small number of patients included in the RCTs, the heterogeneity among treatment protocols, along with the controversial findings and the off-label indication and high costs. Hence, larger prospective long-term RCTs are advisable to better clarify the role and efficacy of this kind of treatment.

DIAGNOSTIC AND THERAPEUTIC FLOW-CHART

Many attempts have been performed in the past 40 years to provide comprehensive and, at the same time, simple flow-charts for both diagnostic and therapeutic purposes. Obviously, these simplifications of the medical act are proportional to the different expertise of the healthcare. The flow-chart depicted in **Figure 1** is only apparently complex. ED is indeed a complex symptom, deeply involving the general quality of life of the patient and of at least one other person. Since our knowledge of the pathophysiological mechanisms, the diagnostic tools, and the therapeutical options is continuously growing, the possible flow charts are growing in complexity. Our final flow-chart aims to help the clinician make a therapeutic choice on the basis of scientific evidence, integrating as much as possible the various therapies available after a detailed diagnostic effort.

CONCLUSIONS

In a recent revision of the process of care model for management of ED, it has been stated that its effective management could be achieved only through a combination of patient risk factor removal or modification and first-line therapies, such as PDE5i, always coupled with counseling and, in selected patients, with psychotherapy, addressing any patient comorbidities known to be associated with ED [197]. Hence, in the statements here presented, SIAMS and the Scientific Societies involved stress the need for a careful and expert diagnostic workup in light of Systems Sexology for defining the treatment goals that must be individualized to restore sexual health and satisfaction to the patient and/or couple and to improve quality of life based on the expressed needs and desires of the patient.

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Systemic risk factors	<ul style="list-style-type: none"> • Organ failure: end stage renal diseases; liver cirrhosis • Rheumatic and/or autoimmune diseases • Life expectancy malignancies • Systemic inflammation: HIV, long term COVID-19 infection
Cardiovascular and respiratory risk factors	<ul style="list-style-type: none"> • Arterial hypertension • Cardiovascular diseases • Chronic obstructive pulmonary disease and sleep apnea
Metabolic risk factors	<ul style="list-style-type: none"> • Obesity • Diabetes mellitus • Dyslipidemia and Gout
Hormonal risk factors	<ul style="list-style-type: none"> • Hypogonadism • Hyperprolactinemia • Hyperthyroidism • Addison's disease • Cushing's Syndrome,
Neurological risk factors	<ul style="list-style-type: none"> • Spinal cord injury • System atrophy • Parkinson's Disease • Multiple Sclerosis • Epilepsy • Peripheral nervous system disorders involving pelvic plexus
Urological risk factors	<ul style="list-style-type: none"> • Lower Urinary Tract Symptoms • Chronic prostatitis/chronic pelvic pain syndrome • Peyronie's disease • Congenital or acquired penile anatomical abnormalities
Toxicological and iatrogenic risk factors	<ul style="list-style-type: none"> • Substance/Drug Abuse • Iatrogenic medical <ul style="list-style-type: none"> -Drugs interfering with testosterone activity/metabolism -Drugs reducing dopamine or increasing serotonin pathway (antipsychotic, antidepressants) -Non selective β-blockers; thiazide diuretics • Iatrogenic surgical: pelvic surgery for malignancy

Psychiatric, psychological and relational risk factors	<ul style="list-style-type: none">• Some psychiatric disorders: schizophrenia, depressive and anxiety disorders, bipolar disorders, post-traumatic stress disorder• Relational problems and couple fitness impairment
Sexual risk factors	<ul style="list-style-type: none">• Hypoactive Sexual desire• Premature ejaculation and ejaculatory disorders• Partner sexual disorders• Infertility

Table 1. Main risk factors associated with erectile dysfunction

1. Because virtually all sexual dysfunctions produce a psychological and/or relational derangement. Hence all EDs are, with some extents, psychogenic
2. Because tools to demonstrated that a particular ED is only generated by the mind (which is the meaning of the term “psycho-genic”) do not exist
3. Because it is based on an obsolete view of mind-body distinctions.
4. Because it disregards knowledge of the neurobiology of “psychological” disorders.
5. Because it disregards the fundamental meaning of “psychosomatic.”
6. Because ED cannot be diagnosed by exclusion.
7. Because ED is not “all in the mind”, but also in vessels, nerves, and hormones
8. Because it adds a negative stigma of mental disorder

Table2. Reasons to avoid the term “psychogenic ED”

	Avanafil	Sildenafil	Vardenafil	Tadalafil
Available doses (mg)	50,100, 200	25, 50, 75, 100	5, 10, 20	5, 10, 20
Available formulation	FCT	FCT, ODT, ODF	FCT, ODT	FCT
Pharmacokinetic proprieties				
Oral bioavailability	-	40%	15%	36%
t _{max} , minutes	30-45	60	60	120
Duration of action (hours)	6	12	12	36
C _{max} , ng/ml (fasting)	871 (100mg)	327	20.9 (20mg)	378 (20mg)
Food effect (high-fat-meal)	t _{max} , increased 1.25 h	t _{max} , increased 1 h	t _{max} , increased 1 h	No significant
t 1/2 (hours)	3-5	3-5	4	17.5
Renal excretion %	21%	<1	1	<0.3
CYP isoenzymes	3A4 and minor contribution of 2C9	3A4 (79%), 2C9 (20%), 2C19 and 2D6 (<2%)	3A4 (major) 3A5 and 2C9 (minor)	3A4
Effect on exposure/clearance, of				
Age	None	Reduced clearance	Reduced clearance	Reduced clearance
Mild renal impairment	None	None	None	Increased exposure
Moderate renal impairment	None	None	None	Increased exposure
Severe renal impairment	No data	Increased exposure	Increased exposure	Increased exposure
Mild hepatic impairment	None	Increased exposure	Increased exposure	None
Moderate hepatic impairment	Reduced exposure	Increased exposure	Increased exposure	None
Severe hepatic impairment	Not studied	Not studied	Not studied	Limited data

Table 3. Pharmacokinetics of the different PDE5 inhibitors. FCT= film coated tablet, ODT= oral dispersible tablet; ODF= oral dispersible film. Adapted from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002581/WC500145206.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000202/WC500049830.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000475/WC500039992.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000436/WC500026318.pdf

Side effects (%)	Sildenafil 100 mg (252)	Tadalafil 20 mg (253)	Vardenafil 20 mg (254)	Avanafil 200 mg (255)
Headache	12	21	21	9.3
Dyspepsia	5	17	6	0
Back pain	-	9	-	0
Nasal congestion	2	5	17	1.9
Sinusitis	-	0	5	3.7
Flushing	10	5	13	3.7
Visual disturbances	4	0	-	0
Myalgia	-	5	-	0

Table 4. Incidence of drug-related side effects as derived from the first published paper dealing with them in the general population

RECOMMENDATION	JUSTIFICATION	REF
Use PDE5i always after a careful diagnosis and management of all possible risk factors	Logically, if the treatment of the underlying condition is sufficient for improving the erectile function, PDE5i is not to be prescribed	181
Ensure PDE5i use within the context of sexual stimulation	PDE5i are not effective without sexual stimulation and frequently not effective with low desire (drug will not cause erection by itself)	182
Take short onset PDE5i 45-60 minutes before sexual activity	Maximal drug concentration is achieved between 30-60 minutes after ingestion	*
Take late onset PDE5i at least 120 minutes before sexual activity	Maximal drug concentration is achieved, with large variability, from 120 minutes after ingestion	183
Take PDE5i on an empty stomach or with a low-fat meal	Certain PDE5Is are more effective when taken without food or a high-fat meal. First-time users should be advised to use any PDE5i in the best condition, i.e. on an empty stomach.	184
Do not change PDE5i or titrate to the maximal dose before 4-6 full attempts in a congruous erotic environment	Changing therapies based on spotty experiences could jeopardize clinical evaluation.	185
Lacking efficacy, change to maximum dose if starting dose does not achieve desired goal	Titration to maximum dose may optimize response rates in patients not satisfied with effects of lower dose	182, 186
Lacking efficacy, change from on-demand dosing to daily dosing	Some patients experienced improved response after switching to a daily-dose formula	187
Lacking efficacy, the association of daily PDE5i, such as tadalafil, with on-demand short-acting PDE5i could be considered	Although off label, several experimental findings demonstrated both the safety and efficacy of this association.	188
Consider the issue of privacy by prescribing PDE5i in the orodispersible film (ODF) formulation.	In several clinical settings, patients may ask for full respect of their privacy in the assumption of PDE5i, which is easily obtained by the ODF formulation.	247, 255
Counseling is mandatory before any treatment of ED	Many patients receive PDE5i without counseling. This is to be considered a major mistake reducing the efficacy of the drugs	189
All pharmacological treatments of ED increase their efficacy if associated with psychotherapy	Each patient with a sexual dysfunction may improve with a psychotherapeutic trial, which is to be considered mandatory only in selected patients.	190

Table 5. Recommendations to Improve Responsiveness to PDE5is (adapted from

ref.256)* [http://www.ema.europa.eu/docs/en_GB/document_library/EPAR -](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002581/WC500145206.pdf)

[_Product_Information/human/002581/WC500145206.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002581/WC500145206.pdf);

[http://www.ema.europa.eu/docs/en_GB/document_library/EPAR -](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000202/WC500049830.pdf)

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[http://www.ema.europa.eu/docs/en_GB/document_library/EPAR -](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000436/WC500026318.pdf)

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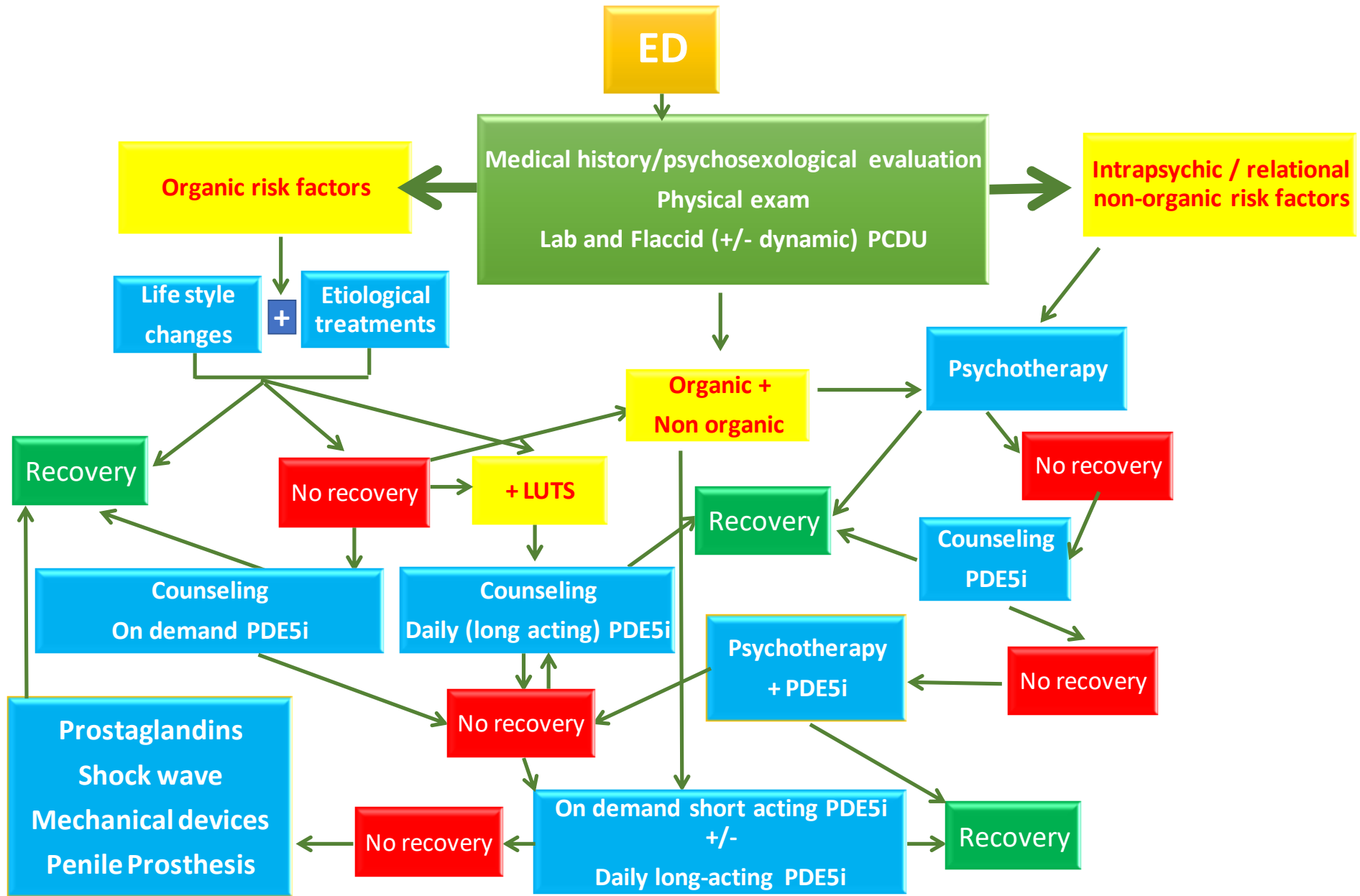


Figure 1. The flow-chart on the management of patients seeking medical care for erectile dysfunction (ED). PCDU= penile color Doppler ultrasound; LUTS= low urinary tract symptoms; PDE5i= phosphodiesterase type 5 inhibitors

CARDIOVASCULAR AGENTS

Class of Dugs	Type of interaction	Clinical effects	Current labeling
<p><i>Nitrates:</i></p> <p>Nitroglycerin Isosorbide dinitrate Isosorbide mononitrate Amyl nitrate “popper” Nitrate</p>	<p>PDE5i-dependent reduction in the breakdown of cGMP induced by organic nitrates leading to a marked increase of cGMP signaling.</p>	<p>Synergic decrease in blood pressure leading to possible individual experiencing hypotension (SBP < 85 mmHg)</p>	<ul style="list-style-type: none"> • Contraindications for all PDE5is • Past use (> 2 weeks) not considered a contraindication • A period \geq 24 hours for short acting PDE5is (<i>avanafil, sildenafil and vardenafil</i>) and up to 48 hours for long acting (<i>tadalafil</i>) recommended against taking nitrates.
<p><i>Antihypertensive agents:</i></p> <ul style="list-style-type: none"> • α-blocker agents Doxazosin Tamsulosin Alfuzosin Terazosin Carvediol (mixed α-blocker) Labetol (mixed α-blockers) • other antihypertensives Selective β-blockers Calcium antagonists Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Diuretics 	<p>Possible increase of hypotensive effects</p>	<p>Synergic decrease in blood pressure leading to possible individual experiencing hypotension (SBP < 85 mmHg)</p>	<ul style="list-style-type: none"> • Precautions for all PDE5is. • PDE5is should be initiated at the lowest recommended dose. • Patients already taking an optimal dose of PDE5 inhibitor the α-blocker should be initiated at the lowest dose. • None
<p><i>Antiarrhythmics</i></p> <p><u>Class 1 A</u> Quinidine Procainamide</p>	<p>QT interval prolongation</p>	<p>Torsade de pointes and ventricular tachycardia.</p>	<ul style="list-style-type: none"> • Precaution for vardenafil. • No limitation for other PDE5i

<u>Class III</u> Sotalol Amiodarone	QT interval prolongation	QT interval prolongation	<ul style="list-style-type: none"> • Precaution for vardenafil. • No limitation for other PDE5i
<u>Class IV</u> Verapamil	CYP3A4 inhibitor	Increase of systemic exposure	<ul style="list-style-type: none"> • Avanafil: precaution and maximum recommended dosage of 100 mg within 48 h after verapamil use • Precaution and possible dosage reduction for other PDE5i

CARDIOVASCULAR AGENTS

Class of Dugs	Type of interaction	Clinical effects	Current labeling
<p><i>Anticoagulant agents</i> warfarin</p>	<p>Substrate of CYP2C9 metabolism</p>	<p>Possible increase in prothrombin time and increased risk of bleeding events.</p>	<ul style="list-style-type: none"> • None for all PDE5i (no significant clinically interactions)
<p><i>Anti-platelet aggregating agents</i></p>	<p>Sildenafil increases inhibitory effects of nitric oxide donors on ADP-dependent platelet aggregation.</p>	<p>Possible increase in bleeding time and increased risk of bleeding events.</p>	<ul style="list-style-type: none"> • Precaution, in particular for sildenafil, for the high risk cardiovascular patient, commonly on multiple anti-thrombotic regiments or on warfarin
<p><i>Statins:</i></p>	<ul style="list-style-type: none"> • Increase the expression of eNOS • Activation of the serine/threonine kinase Akt which in turn, phosphorilates eNOS • Inhibition of the RhoA/RhoA-kinase pathway. 	<p>Possible improvement of PDE5is outcomes</p>	<ul style="list-style-type: none"> • None

ORAL HYPOGLYCEMIC AGENTS

Class of Dugs	Type of interaction	Clinical effects	Current labeling
<i>Hypoglycemic drugs</i> Sulfonylureas Benzoic acid derivates	Not reported	Not reported	<ul style="list-style-type: none"> • None
<i>Antihyperglycemic drugs</i> Biguanides α -Glucosidase inhibitors Thiazolidinediones	Not reported	Not reported	<ul style="list-style-type: none"> • None

ANTIDEPRESSANTS

<i>SSRI:</i> Fluvoxamine Fluoxetine	CYP3A4 inhibitors	Increase of systemic exposure	<ul style="list-style-type: none"> • Precaution: starting dose of sildenafil 25 mg is suggested for patients on fluvoxamine therapy • No specific studies for tadalafil and vardenafil but similar precautions should be advised. • No specific studies have been reported for Fluoxetine • Contraindication for simultaneous use of avanafil and nefazodone
Citalopram Escitalopram Paroxetine Sertraline Venlafaxine	No significant effects on CYP3A4	None	<ul style="list-style-type: none"> • None.
<i>iMAO:</i>	Possible additive hypotensive effects	Possible individual experiencing hypotension	<ul style="list-style-type: none"> • Precaution for all PDE5is

ANTIEPILEPTICS

Phenobarbital Phenytoin Carbamazepin	CYP3A4 inducers	Reduction of systemic exposure	<ul style="list-style-type: none"> Potentially required higher dose of PDE5is
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CHEMIOTERAPICS

Class of Dugs	Type of interaction	Clinical effects	Current labeling
<i>Macrolid antibiotics</i> Erythromycin Clarithromycin Troleanddomycin	CYP3A4 inhibitors	Increase of systemic exposure	<ul style="list-style-type: none"> Sildenafil: precaution and dose reduction. Vardenafil: precaution, not to exceed a single 2.5-5mg dose of vardenafil in a 24-hour period. Tadalafil: precaution not to exceed a single 10 mg dose, and should not be taken more than once for 72 hour-period. Avanafil: controindication concomitant use with claritromycin and troleandromycin, precaution and maximum recommended dosage of 100 mg within 48 h after eritromycine use
Azithromycin	Not involved in CYP3A4	None	<ul style="list-style-type: none"> None
<i>Rifampin</i>	CYP3A4 inducer	Reduction of systemic exposure	<ul style="list-style-type: none"> Precaution: potentially required higher dose of PDE5is.
<i>Azole antifungals</i> Ketoconazole Itraconazole Fluconazole Voriconazole	CYP3A4 inhibitors	Increase of systemic exposure	<ul style="list-style-type: none"> Sildenafil: precaution and dose reduction. Vardenafil: precaution, not to exceed a single 2.5-5mg dose of vardenafil in a 24-hour period. Tadalafil: precaution not to exceed a single 10 mg dose, and should not be taken more than once for 72 hour-period. Avanafil: controindication with use of ketoconazole, itraconazole and voriconazole, precaution not to exceed a single 100 mg dose, and should not be taken more than once for 48 hour-period with fuconazole

<ul style="list-style-type: none"> • <i>Antiretroviral protease inhibitors</i> <p>Ritinoar Saquinoar Tipranavir Indinavir Fosamprenavir</p>	<p>CYP3A4 inhibitors</p>	<p>Increase of systemic exposure</p>	<ul style="list-style-type: none"> • Sildenafil: precaution not to exceeded a single dose of 25 mg of sildenafil in 48-hour period. • Vardenafil: precaution, not to exceed a single 2.5-5mg dose of vardenafil in a 24-hour period. • Tadalafil: precaution not to exceed a single 10 mg dose, and should not be taken more than once for 72 hour-period. • Avanafil: contraindication with use of ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, precaution not to exceed a single 100 mg dose, and should not be taken more than once for 48 hour-period with aprenavir, fosamprenavir
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H2 INHIBITOR/ANTIACID AGENTS

Class of Dugs	Type of interaction	Clinical effects	Current labeling
<i>H2 inhibitors:</i> Cimetidine Ranitidine	Non specific CYP inhibitor Not involved in CYP metabolism	Increase of systemic exposure None	<ul style="list-style-type: none"> • Precaution: potentially required lower dose of PDE5is • None.
<i>Antacids</i> Aluminum hydroxide/magnesium hydroxide	Reduction of the tadalafil absorption by 30% No effect on vardenafil and sildenafil absorption	Reduction of systemic exposure	<ul style="list-style-type: none"> • Precaution: potentially required higher dose of tadalafil

Supplementary Table 1. Principal phosphodiesterase 5 (PDE5) inhibitor- drug interaction and current labeling.