ERECTILE FUNCTION

Misdiagnosis And Undertreatment Of Erectile Dysfunction In The Portuguese Primary Health Care

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ABSTRACT

Introduction: The importance of erectile dysfunction (ED) diagnosis and treatment has been highlighted since the early 2000s. However, nearly 20 years after the first phosphodiesterase 5 inhibitor (PDE5i) was marketed, underdiagnosis and undertreatment of ED in the primary health care setting may still be present.

Aim: To assess the relative frequency of patients who are medically treated for ED before referral to specialized urology care. The secondary objectives were to evaluate possible reasons for non-treatment prior to referral and other signs of undertreatment, namely cardiovascular risk assessment and antihypertensive treatment.

Methods: 200 male patients referred for ED to specialist urology care by general practitioners were screened after consent between January 2016—December 2018. A full standardized medical and sexual history were taken. Previous medical treatment of ED, namely pharmacologic name and dosages, and cardiovascular risk factors were noted.

Main Outcome Measures: Of the 115 included patients, only 33.9% of patients had already taken PDE5i before referral, and none had taken alprostadil by intracavernous route.

Results: The mean patient age was 58.68 ± 10.01 years old. Only 45.2% had been prescribed the highest dose of PD5i. From the remaining untreated patients, only 19.7% had ≥3 cardiovascular risk factors, including 5.6% of patients who also presented moderate-to-severe stable or unstable angina requiring a stress test or cardiology assessment before treatment. Regarding the 54 patients with medical history of arterial hypertension, 43.4% and 30.2% were treated for hypertension with a diuretic and a beta blocker, respectively.

Conclusion: More focus on the primary healthcare continuous medical education regarding sexual dysfunction, namely ED, is needed because major undertreatment of ED is still present because low prescription of PD5i before referral is noted. **Morgado A, Moura ML, Dinis P, et al. Misdiagnosis And Undertreatment Of Erectile Dysfunction In The Portuguese Primary Health Care. Sex Med 2019;7:177—183.**

INTRODUCTION

The importance of erectile dysfunction (ED) diagnosis and treatment has been highlighted since the early 2000s due to the finding of an independent association between ED and coronary artery disease (CAD).[1–4] Moreover, ED often precedes symptomatic CAD or its diagnosis, and ED is often described as a sentinel symptom of CAD.[5] Furthermore, ED is known to be a side effect of common medications for diseases, such as arterial hypertension, and ED has a known effect on the quality of life.[6–9] Moreover, its treatment has been shown to improve not only erectile function but also the quality of life[10]; thus, its diagnosis and treatment should be sought.

In Portugal, ED is a prevalent, age-related disease. A national survey published in 2011 disclosed that 26.0% of men >60 years old reported erection problems.[11] The prevalence of ED and the availability of safe and efficacious first-line treatment has necessarily changed ED treatment from an exclusive specialty in either urology or psychiatry to also include primary health care providers. This shift in paradigm and the acknowledgement of the limited opportunities to learn sexual medicine in medical school and

residency,[12] as well as the lack of sexual history taking by general practitioners (GPs), has led to the development of widely available clinical practice recommendations, screening questionnaires, and continuous medical education programs to improve the quality of care provided.[13,14] However, nearly 20 years after the first phosphodiesterase 5 inhibitor (PDE5i) was marketed, these issues concerning ED diagnosis and treatment may still be present.

In the beginning of 2011, a questionnaire was completed by 50 Portuguese GPs. Despite 98.0% agreeing that sexual dysfunction is an important public health issue, only 15.5% actively asked their patients about sexual dysfunction, whereas 58.0% would rather refer to specialist care than start treating a sexual dysfunction.[15] Patients complaining of ED are often perceived by GPs as "too ill" to address sexual issues.[16] Frequently, GPs are afraid of intrusion and inadequacy when addressing issues of an intimate and private nature, only seldom or occasionally initiating a discussion about sexual concerns.[17] Moreover, Portuguese GPs express a high need for continuous training in sexual medicine, and >50% consider that their degree is not an adequate source of training.[18] Thus, even though sexual concerns are prevalent among patients, they are rarely brought up during consultation.[19] These concerning reports indicate that there is still a need for both graduate and postgraduate training in this area. This signals a possible underdiagnosis and undertreatment of sexual dysfunction in the primary health care setting.

Our group hypothesized that this issue is still existent, so we decided to examine why and how patients with ED are referred by GPs to specialist urology care. The primary aim was to assess the relative frequency of patients medically treated for ED before referral to specialized urology care. The secondary aims were to evaluate possible reasons for non-treatment previous to referral and other signs of undertreatment, namely cardiovascular risk assessment and antihypertensive treatment.

MATERIAL AND METHODS

After approval by the hospital's ethical committee, 200 consecutive male patients referred for ED to specialist urology care by GPs were intended for screening between January 2016—December 2018. The main reason for GP referral was established through referral letter review by 2 different reviewers. After consent was obtained, a full standardized medical and sexual history was taken. A main diagnosis of sexual dysfunction was formulated according to the criteria from the 10th revision of the International Statistical Classification of Diseases and Related Health Problems. All patients with an unconfirmed main diagnosis of ED and history of penile surgery other than circumcision were excluded. Cardiovascular risk factors and concomitant medications were noted. Previous medical treatment for ED was also noted, namely pharmacologic name, dosage, and number of pills taken. Included patients were also asked to complete a translated validated version of the brief International Index of Erectile Function (IIEF-5).[20] Patients completed a basic

diagnostic evaluation for ED with physical evaluation, including blood pressure, laboratory analyses when appropriate, and cardiac risk stratification according to the second and third Princeton Consensus.[21] Laboratory analyses consisted of 2 morning serum total testosterone and fasting glucose plus lipid profiles, if not previously performed in the last 6 months.

In the data analysis, patients were stratified according to previous medical treatment status for ED. For previously treated patients, the relative frequencies of pharmacologic name and dosage of the treatments were determined. Previously untreated patients were further stratified in cardiovascular risk groups, according to the aforementioned consensus criteria, and relative frequencies were also calculated. Patient eligibility for immediate first-line ED treatment was defined as the absence of absolute contraindication for first-line treatment with PDE5i. Low cardiovascular risk was defined by ≤2 cardiovascular risk factors, excluding sex. Absolute contraindication for treatment with PDE5i was defined as hypersensitivity to PDE5i or concomitant regular or intermittent use of nitric oxide donors. Patient characteristics, including cardiovascular risk factors, were compared between previously treated and non-treated patients. Patients were asked permission to enroll in a 6-month voluntary follow-up. If agreed, the cardiovascular risk stratification result and treatment response as assessed by IIEF-5 were noted at the 6-month follow-up. Undertreatment was defined as no previous treatment for ED before referral, no treatment with a PDE5i on the highest dosage before referral, failure to optimize concomitant medication, namely antihypertensives, before referral or in patients previously treated with a PDE5i inhibitor on the dosage but resolution of symptoms at 6 months' follow-up.

All data were collected and assessed using SPSS (version 24 SPSS Inc, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to test parameter distribution. All continuous variables with normal distribution are expressed as the mean ± SD, and non-normally distributed variables are expressed by the median (25th—75th quartiles). The differences between groups were evaluated using the unpaired 2-sided Student t-test for normal distribution and the Mann-Whitney U test for all other distributions. Univariate and multivariate analyses were performed to evaluate differences in characteristics between treatment groups. Statistical significance was considered at a P-value <.05.

RESULTS

From the 200 patients intended for screening, 179 were effectively screened, because 21 patients missed their appointment. Overall, 115 patients fulfilled all the inclusion and exclusion criteria and agreed to participate. There was an important misdiagnosis of ED with 22.3% of the valid screens excluded from participating for a main diagnosis other than ED. Furthermore, 8.4% of those referred demonstrated spontaneous resolution of symptoms at the time of consultation (Table 1). The most common misdiagnosis was premature ejaculation (PE), with 10.6% of valid screened patients receiving this diagnosis.

Table 1. Description of patients excluded from the primary analysis

	% of row total (n)
Excluded for main diagnosis other than ED	20.9% (40)
Premature ejaculation	10.6% (19)
Peyronie's disease	3.4% (6)
Diminished libido	3.4% (6)
Anorgasmia	1.7% (3)
Retrograde ejaculation	1.1% (2)
Anteporta ejaculation	1.1% (2)
Painful ejaculation	0.6% (1)
Low volume ejaculation	0.6% (1)
Spontaneous resolution of symptoms	8.4% (15)
Excluded for previous penile surgery	2.8% (5)
Penile prosthesis	2.8% (5)
Refusal to participate	2.0% (4)

Table 2. Patient characteristics

Age, mean ± SD	58.6 ± 10.0 y
Ethnicity	
White, % (n)	99.1% (114)
Black, % (n)	0.9% (1)
Marital status	
Single, % (n)	5.2% (6)
Married, % (n)	67.0% (77)
Divorced, % (n)	14.8% (17)
Widowed, % (n)	13.0% (15)
Education	
Until 4th grade, % (n)	49.6% (57)
Until 9th grade, % (n)	35.6% (41)
Until high school graduation, % (n)	9.6% (11)
Some college or college degree, % (n)	5.2% (6)
Work	
Employed, % (n)	64.3% (74)
Unemployed, % (n)	5.2% (6)
Retired, % (n)	30.4% (35)
Body mass index, mean ± SD	28.6 ± 3.9 kg/m^2
Baseline IIEF-5, mean ± SD	10.8 ± 4.3
Number of CV risk factors, mean ± SD	1.84 ± 1.34
Arterial hypertension, % (n)	48.6% (54)
Dyslipidemia, % (n)	44.1% (49)
Diabetes mellitus, % (n)	39.6% (44)
Obesity, % (n)	32.4% (22)
History of CAD, % (n)	10.1% (11)
Active smoking, % (n)	30.7% (27)
Mental health disorder, % (n)	9.2% (10)

CAD = coronary artery disease; CV = cardiovascular; IIEF-5 = International Index of Erectile Function.

The mean age of the patients was 58.68 ± 10.01 years old, and the mean IIEF-5 score was 10.88 ± 4.37. The majority of patients had studied until fourth grade (49.6%) or ninth grade (35.6%) and were actively working (64.7%); 67.0% were married. Additional sociodemographic data are described in Table 2. Other morbid conditions, such as hypertension (48.6%), dyslipidemia, (44.1%), diabetes mellitus (39.6%), history of CAD (10.1%), active smoking status (30.7%), and obesity (32.4%) were common in this population (Table 2). Regarding new diagnosis, only 3 patients (7.9%) were diagnosed with arterial hypertension, whereas there were 0 (0.0%) with diabetes mellitus and only 5 (8.9%) with dyslipidemia.

Regarding the 54 patients with medical history of arterial hypertension, 43.4% and 30.2% were treated for hypertension with a diuretic and a beta blocker, respectively. In addition, almost two-thirds (64.8%) were treated with either a diuretic or a beta blocker, whereas only one-third (37.5%) of the patients treated with a beta blocker were receiving nebivolol.

Regarding lifestyle changes, only 26.0% indicated that lifestyle changes had also been suggested with medical treatment, and 4.3% indicated that only the former was suggested. Regarding cardiovascular risk factor optimization, 86.8% had normal or controlled blood pressure, whereas 84.2% had normal fasting glycemia or controlled glycated hemoglobin. Additionally, 71% had a normal or controlled lipid profile.

Regarding previous medical treatment for ED, only 33.9% were previously treated for ED and, if all screened patients were considered, only 29.0% of patients would have been previously treated for ED. The most common previous treatment for ED was sildenafil (42.1%). 45.2% of patients were treated at the highest dosage of the PDE5i prescribed (Table 3). Moreover, only 2 patients (5.2%) were on alprostadil cream, and no patient had any form of intracavernous treatment. Only 1 (2.5%) patient had been treated with a daily low-dose tadalafil. All except 1 patient were referred for lack of PDE5i efficacy. 26 patients agreed to repeat an IIEF-5 at 6 months of treatment with PDE5i

at the highest dosage. The majority (73.0%) had resolution of symptoms as assessed by a normal IIEF-5 score (>21).

Regarding previously non-treated patients (66.1%, 76 patients), concomitant cardiovascular risk factors were analyzed. Only 19.7% of the aforementioned group presented ≥3 cardiovascular risk factors, excluding sex (Table 4), and only another 5.6% presented moderate-to-severe stable or unstable angina.

When previously treated patients were compared with untreated patients, there were no statistically significant differences in age, body mass index, baseline IIEF-5 score, and number of cardiovascular risk factors. There was no statistically significant difference in the distribution of ethnicity, marital status, education, work, hypertension, dyslipidemia, diabetes mellitus, history of CAD, smoking status, or obesity in univariate or multivariate analyses (Table 5).

DISCUSSION

Currently, there is still a lack of knowledge regarding the relationship between primary health care and specialized urology care in ED diagnosis and treatment. The few existent reports only address GP habits and intentions regarding ED diagnosis

Table 3. Previous treatment by pharmacologic name, dosage, and number of pills/tries for erectile dysfunction.

	Relative frequency, % (n)
Pharmacologic name	
Sildenafil	42.1% (16)
Avanafil	23.6% (9)
Tadalafil	26.3% (10)
Vardenafil	18.4% (7)
Alprostadil cream	5.2% (2)
PDE5i dosage	
Highest	45.2% (14)
Intermediate	35.5% (11)
Lowest	19.3% (6)
Reason for referral	
Lack of efficacy of PDE5i	97.4% (37)
Adverse effect of PDE5i	2.6% (1)

PDE5i = phosphodiesterase 5 inhibitor.

and treatment.[15,16,18,22] These reports often highlight discomfort, lack of knowledge, and time constraints from doctors to address sexual dysfunctions. Since the introduction of the first PDE5i in the late 1990s, there has been huge support from the pharmaceutical industry to gather medical and patient information regarding ED and other sexual dysfunction. There was always a special focus in the primary health care training, because ED was and still is a prevalent disease. Hopefully, some of the early conclusions regarding the primary health care setting may not hold true after the golden years of the pharmacologic "sex revolution."

In the present study, rather than intentions and habits of GPs, we have looked at their actions appraising why and how patients with ED are referred to specialized urology care in real clinical practice. 1 very important topic is covered in this study, the possible undertreatment of ED.

It is known that male sexual dysfunction, especially ED and PE, can sometimes be confounded by both patients and doctors.[23] When looking at excluded patients, the majority were

Table 4. Cardiovascular risk factors in previously untreated patients (n = 76 patients)

	% of row total (n)
Arterial hypertension	44.6% (33)
Dyslipidemia	40.8% (31)
Diabetes mellitus	36.8% (28)
Obesity	14.4% (11)
History of CAD	11.8% (9)
Active smoking	26.3% (20)
Number of CV risk factors	
0	23.7% (18)
1	25.0% (19)
2	31.6% (24)
≥3	19.7% (15)

CAD = coronary artery disease; CV = cardiovascular.

excluded, as the main diagnosis was other than ED, with PE being the most common misdiagnosis. The magnitude of the latter does not seem to be discordant with data from other studies regarding both misdiagnosis or co-diagnosis of ED and PE.[24,25] Given the limited time today's general practitioners have with a patient and patient's limited ability to report and describe symptoms, among other reasons, the complaint of difficulty in maintaining an erection can often be left unexplored and straightforward interpreted as a symptom of ED, rather than PE. Erectile function was normal in all of these patients.

Unfortunately, there is clearly a major undertreatment of ED before referral. The common patient of our study is a middle-aged man with a couple of cardiovascular risk factors and the consequent treatment medication. Some antihypertensive medications are known to cause or aggravate ED,[26] namely thiazide diuretics, loop diuretics, and beta blockers, with the sole exception of nebivolol,[27,28] Other classes seem to have no effect on erectile function, and angiotensin II receptor blockers might even have a positive effect.[29] In Portuguese recommendations to GPs, thiazide diuretics, renin-angiotensin system modulators, and calcium channel blockers are all first-line options, whereas beta blockers should only be used in cases of concomitant heart disease or in younger patients.[30] Moreover, GPs are reminded that side effects and patient-associated conditions should be considered when initially choosing an antihypertensive class of medication.

Before starting medical treatment or referral, it is important to consider lifestyle changes and cardiovascular risk optimization, to review patient medication thoroughly, and, if possible, to remove or change medication that is known to cause or aggravate ED, such as antihypertensive agents. These interventions alone have been shown to improve ED[31]. Almost half of our population had a medical history of arterial hypertension, and, from these patients, almost two-thirds were treated with either a diuretic or a beta blocker for arterial hypertension. Most of those patients on diuretics were on thiazides, whereas only one-third of those treated with a beta blocker were on nebivolol. There is clearly margin for improvement, because both diuretics and beta blockers can often be swapped for other antihypertensive classes with a better side-effect profile on erectile function. In the specific case of beta blockers, these can even be replaced by nebivolol, if needed, with a better side-effect profile.[32,33]

Although lifestyle changes were only reportedly suggested to roughly one-third of the patients, the vast majority had its cardiovascular risk factors optimized as assessed by blood pressure, glycemic control, and the lipid profile, and only one-third were still active smokers. Given the limited time available by Portuguese GPs on appointments, the modification of complaints associated with high morbidity/high mortality, rather than the limited to quality-of-life ones, is often a major concern in their daily practice. However, this usually comes at the expense of medical treatment and not lifestyle intervention, as shown by the low reported suggestions for lifestyle intervention.

Table 5. Comparison between previously treated and untreated for erectile dysfunction patients

	Treated (39)	Non-treated (76)	P value Univariate	Multivariate
Age, mean ± SD	61.0 ± 8.4 y	58.3 ± 10.3 y	.155	.229
Ethnicity			.476	.347
White, % (n)	100.0% (39)	98.7% (75)		
Black, % (n)	0.0% (0)	1.3% (1)		
Marital status			.782	.728
Single, % (n)	2.6% (1)	6.6% (5)		
Married, % (n)	69.2% (27)	65.8% (50)		
Divorced, % (n)	15.4% (6)	14.6% (11)		
Widowed, % (n)	12.8% (5)	13.2% (10)		
Education			.670	.943
Until 4th grade, % (n)	51.3% (20)	48.7% (37)		
Until 9th grade, % (n)	25.6% (10)	23.7% (18)		
Until high school graduation, % (n)	18.0% (7)	22.3% (17)		
Some college or college degree, % (n)	5.1% (2)	5.3% (4)		
Work			.634	.689
Employed, % (n)	61.6% (24)	65.8% (50)		
Unemployed, % (n)	5.1% (2)	5.3% (4)		
Retired, % (n)	33.3% (13)	28.9% (22)		
Body mass index, mean ± SD	28.6 ± 2.6 kg/m^2	28.6 ± 4.5 kg/m^2	.949	.872
Baseline IIEF-5, mean ± SD	10.8 ± 4.5	10.9 ± 4.3	.922	.162
Number of CV risk factors, mean ± SD	2.06 ± 1.73	1.37 ± 1.32	.242	.165
Arterial hypertension, % (n)	53.8% (21)	44.6% (33)	.207	.753
Dyslipidemia, % (n)	48.7% (19)	40.8% (31)	.280	.373
Diabetes mellitus, % (n)	43.5% (17)	36.8% (28)	.315	.385
History of CAD, % (n)	5.1% (2)	14.4% (11)	.191	.347
Active smoking, % (n)	17.9% (7)	11.8% (9)	.556	.517

CAD = coronary artery disease; CV = cardiovascular; IIEF-5 = International Index of Erectile Function.

Only roughly one-third of our population has been previously treated for ED. This relative frequency is clearly low. As mentioned, ED is a prevalent disease, and effective, safe, and affordable medical treatment is widely available; thus, it would be expected that the largest burden of ED care would rely on the GPs, and only refractory ED patients would be referred to specialized urology care. Although it is a matter of current debate regarding whether GPs or only urologists should start second-line intracavernous therapy, it is clear that, in the absence of contraindication, PDE5i at the highest dosage should be tried and tested, preferably ≥8 times before a conclusion is drawn. In the present study, only 45.2% of previously treated patients were at the highest dosage of PDE5i, whereas no patient was treated with any intracavernous treatment. These data possibly reflect premature referral to specialized care rather than a true lack of response to PDE5i in some patients and indicate undertreatment of ED, because >50% of the patients did not receive appropriate treatment at the highest dosage approved. Unfortunately, few valid answers were noted on the number of pills taken, but the majority reported having only tried ≤4 pills before referral (data not shown). Interestingly, when retreated with PDE5i at the highest dosage, most of the 26 patients who agreed to repeat the IIEF-5 at 6 months had a normal IIEF-5 score. Altogether, these data further underline that, even in previously treated patients, there is undertreatment, either in the form of insufficient attempts, inadequate dosage, or poor patient education on how and when to take PDE5i.

Among the several barriers GPs face regarding not discussing sexual health problems with CAD patients, a patient perceived as "too ill" for treatment was 1 of the most common replies in 1 report,[16] even though PDE5i is currently well established for cardiovascular safety. In our study, cardiovascular risk factors were common among previously non-treated patients (Table 4). However, roughly one-quarter did not present any cardiovascular risk factor, excluding sex, and even fewer presented ≥3 risk factors or moderately stable or unstable angina requiring a stress test or a cardiologist evaluation. Thus, the majority of patients could have probably been treated for ED with PDE5i, possibly avoiding referral for specialized care.

If successful treatment had occurred in previously treated patients, a selection bias would have been observed, because fewer organic ED patients would have responded to treatment, leaving possibly less-healthy patients for referral. However, there was no statistically significant difference between previously treated and

untreated patients, which hints at possible undertreatment and premature referral. Additionally, 26 of the initial 48 previously treated patients were treated with PDE5i for 6 months, and the majority had resolution of symptoms as assessed by the IIEF-5 score.

To our knowledge, the present study is the first to assess GP actions rather than intentions or habits for ED care in a prospective manner, with almost 200 patients screened, and roughly half included. However, our study presents some limitations, because it can suffer from recall bias regarding previous ED treatment. After permission by the patient, the patient chart and past prescription history were reviewed and double-checked with patients to minimize this potential bias. Even though our center is a tertiary academic hospital with a vast area of influence, our study still stands as a single-center study, and local health policies might influence results, which may limit generalizability. Moreover, the study population is relatively small, so relative frequencies can suffer from bias, whereas comparisons can present type 2 errors. However, the study population is comparable in bio-socio-demographic data from a much larger Portuguese study in ED patients treated in primary health care [34], which adds validity to our sample data. The study could have also collected information regarding the GP profile to establish further comparisons and conclusions.

CONCLUSIONS

The present study clearly shows that a sizable proportion of patients with ED are being undertreated in the primary health care setting, as shown by the low or inadequate prescription of PDE5i before referral. Moreover, patient-related cardiovascular risk factors do not seem to be the motive for undertreatment, because the majority of non-treated patients lack a formal contraindication for ED treatment.

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