ORIGINAL RESEARCH—ERECTILE DYSFUNCTION

Undertreatment of Erectile Dysfunction: Claims Analysis of 6.2 Million Patients

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ABSTRACT

Introduction. Prior research conducted on treatment of erectile dysfunction (ED) has been derived from surveys involving relatively small populations of men. There are needs for large population-based studies in this area. Our study addresses that need.

Aim. The aim of this study was to characterize ED treatment among a large population of men.

Methods. Patients ≥30 years in commercial insurance dataset with diagnosis code for ED during 12-month period ending June 2011 were identified. Men were considered "treated" if prescription was filled for phosphodiesterase type 5 inhibitor (PDE5i), injection or urethral prostaglandins, or androgen replacement (ART) during study period. "Untreated" patients received the diagnosis but did not fill prescription. Statistical analyses were used to compare prescription frequency with clinical characteristics, including age and comorbidities.

Main Outcome Measures. ED treatment rates among large population of insured men, treatment types employed, patient demographics, associated medical comorbidities of this population, and prescriber details were the main outcome measures.

Results. Only 25.4% of 6,228,509 men with ED were treated during study period. While PDE5is were the most commonly prescribed medical therapy (75.2%), ART was utilized as monotherapy or in combination therapy in 30.6% of men. ART was significantly ($P < 0.0001$) more frequently used in men <40 and >65 years. Although ED frequency was associated with increased age and number of comorbidities, men >60 years were significantly ($P < 0.0001$) less likely to be treated compared with men aged 40–59 years. Additionally, treatment frequency did not vary as a function of number of comorbidities. However, compared with men with prostate cancer, men with comorbid hypogonadism, sleep disorders, benign prostatic hyperplasia, or components of metabolic syndrome were ($P < 0.0001$) more likely to be treated.

Conclusions. Despite high prevalence of ED with age and comorbidities, most men continue receiving no treatment. Although benefits of medical intervention for ED are well-recognized, many barriers to treatment continually exist including physician, patient and partner preference and knowledge. **Frederick LR, Cakir OO, Arora H, Helfand BT, and McVary KT. Undertreatment of erectile dysfunction: Claims analysis of 6.2 million patients. J Sex Med 2014;11:2546–2553.**

Key Words. Erectile Dysfunction; Phosphodiesterase 5 Inhibitors; Treatment; Comorbidity; Hypogonadism; Medical Intervention of Erectile Dysfunction

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Introduction

Erectile dysfunction (ED) is defined as the consistent inability to attain or maintain an erection of sufficient quality to permit satisfactory sexual intercourse [1]. According to estimates from the 2001–2002 National Health and Nutrition Examination Survey, ED affects 18 million men in the United States or 18.4% of the male population aged ≥20 years. Worldwide estimates suggest that the prevalence of ED will reach 322 million men by the year 2025 [2,3]. It is well-known that the frequency of ED increases as a function of advanced age. For example, the prevalence of moderate to severe ED among men aged <50 years and between 70 to 79 years was 15% and 34%, respectively [4]. In addition, the prevalence of ED has been associated with the prevalence of many different medical conditions. Specifically, ED may share a common pathologic mechanism with metabolic syndrome [5], lower urinary tract symptoms (LUTSs) [6,7], cardiovascular disease [8], central neurologic processes, diabetes mellitus [9], and other endocrine disorders, including hypogonadism.

Goal-directed treatment is essential for the proper management of ED. This takes into account that the patient and partner are involved in the clinical decision-making processes. In dealing with organic ED, management typically progresses from phosphodiesterase type 5 inhibitors (PDE5is) to intracavernous or intraurethral prostaglandin therapies to surgical interventions. PDE5is are often considered to be the first-line treatments and consist of sildenafil, vardenafil, tadalafil and avanafil. Second-line therapies include localized injections to the penis (prostaglandin E1 [PGE1], papaverine, phentolamine), intraurethral PGE1 pellet injections, or vacuum erection devices. Androgen replacement therapy (ART) is another treatment option that is recommended for men with ED who have a confirmed concurrent low-level bioavailable testosterone. It is believed to assist in treatment by upregulating nitric oxide synthase and augmenting the endogenous NOS-NO/cGMP pathway. This restores the normal molecular cascade and improves the response to other therapies (i.e., PDE5i) that improve ED through proper homeostasis [8–10].

It has been shown that ED negatively impacts the quality of life (QoL) and sexual satisfaction of both the patient and partner; while medical and surgical therapies improve these parameters. Despite overwhelming evidence supporting the benefits of medical therapy, there are many barriers to ED treatment. These barriers include cost, severity of ED, the severity of co-morbidities, and patient, partner, and physician preferences.

To date, most of the research conducted on ED treatment frequencies has involved relatively small population-based samples or special disease groups. These studies have suggested that only a small percentage (ranging from 11.6 to 34.4%) of men with ED undergo treatment [11,12]. Based upon this, it was of interest to determine if the medical treatment choices, frequencies of therapies, associated comorbidities, and/or type of health care provider impact prescription frequencies in a large, contemporary population of men with ED.

Materials and Methods

The IMS Health patient claims dataset encompassed a 1-year time period ending in June 2011. This dataset included integrated administrative insurance claims from over 85 different national private health care plans in the United States and contained information on >43.8 million men of all ages. IMS Health is a company that provides information, services, and technology for the health care industry. It is the largest vendor of U.S. physician prescribing data. Men included in the study were ≥30 years with a current International Classification of Diseases, 9th version (ICD-9) diagnosis code for ED (307.72, 607.84). This was any diagnosis, not just a new diagnosis. Given that there is a separate code for premature ejaculation, these patients were excluded. Medication use was recorded for all ED medical therapies at the generic level as well as the drug-class level. Medications for ED included the PDE5i (e.g., sildenafil, vardenafil, and tadalafil), the intracavernous or transurethral injections (e.g., alprostadil, phentolamine, and papaverine), and ART. Avanafil was excluded from the analysis as it was only recently approved by the Food and Drug Administration. We did not include device therapies such as penile prosthesis and vacuum erection devices in our analysis. We also documented subjects' comorbidities using ICD-9 codes for 12 different comorbidities including hypertension (401.x–404.x), dyslipidemia (272.xx), LUTSs (600.xx), benign prostatic hyperplasia (596.0, 788.2x), diabetes mellitus (250.xx), arthritis (710.x–719.x), cardiovascular disease (410.x–414.x, 440.x), hypogonadism (257.2), prostate cancer (185.x), sleep disorders (327.xx), peripheral vascular disease (443.xx), and multiple sclerosis (340.xx).

For the purposes of the study, patients with a diagnosis of ED who filled a prescription for an ED medication during the study period were categorized as "treated"; those who did not fill a prescription for an ED medication despite receiving the diagnosis were classified as "untreated." Those who had a diagnosis of ED were then analyzed by treatment rate, treatment type, prescribing physician, and comorbidity status. Any patients who putatively filled a prescription after the 1-year period were considered as "untreated." Statistical analyses (SAS version 9.2, SAS, Cary, NC, USA) using Armitage chi square analysis test for trend were used to compare the frequencies of medical therapies as a function of age and comorbidities. Funding for this project came from the SIU Urology Endowment Fund and the Havana Day Dreamers Foundation.

Results

The IMS Health dataset had 87,600,000 million covered lives. Of the 6,228,509 men within the IMS Health dataset with a diagnosis of ED, 1,583,003 men (25.4%) were "treated" and 4,645,506 (74.6%) were "untreated." Analysis of the frequency of ED medical therapies among "treated" men demonstrates that the PDE5i class is prescribed at a significantly ($P < 0.0001$) greater frequency compared with all other ED therapies (Figure 1). Analysis of the distribution of treatments include: phosphodiesterase 5 inhibitors (PDE5i) (75.2%), ART (30.6%), PGE1 injectables (1.2%), PGE1 intra-urethral pellets (0.8%), and papaverine or phentolamine (0.6%). The distribution of PDE5is was sildenafil (40.7%), tadalafil (29.9%), and vardenafil (11.3%) (Figure 1). The majority of men treated with ART (n = 333,080; 68.8%) had a co-diagnosis of hypogonadism.

There was an increased frequency of ED diagnosis as a function of age. The frequency of ED with respect to age was 8.2% (age <40), 16.3% (age 40–49), 27.7% (age 50–59), and 47.8% (age >60). However, treatment frequency did not increase with increasing age. There was a significantly ($P < 0.0001$) decreased frequency of treatment among the youngest (<40 years; 25.5%) and oldest age groups (>60 years; 22.1%) compared with men between the ages of 40–59 years (31.0%) (Figure 2). This was most evident in the subgroup of men ≥65 years (n = 2,032,981), as only 17.5% of this age group were treated during the study period.

Evaluation of medical therapy as a function of age group demonstrates that the PDE5is were the most commonly filled prescription in every age group (Figure 3). While the overall proportion of men treated with injectable therapies was infrequent (<2%), their frequency generally increased with advancing age ($P < 0.001$, Armitage chi square analysis test for trend). There was a significant difference in the frequency of ART prescribed based upon age group, as men <40 and ≥65 years were significantly ($P < 0.0001$) more likely, while men age 60–64 years were significantly less likely to be treated with ART compared with the other age groups.

We next compared the frequency of ED with the presence of 12 commonly associated comorbidities

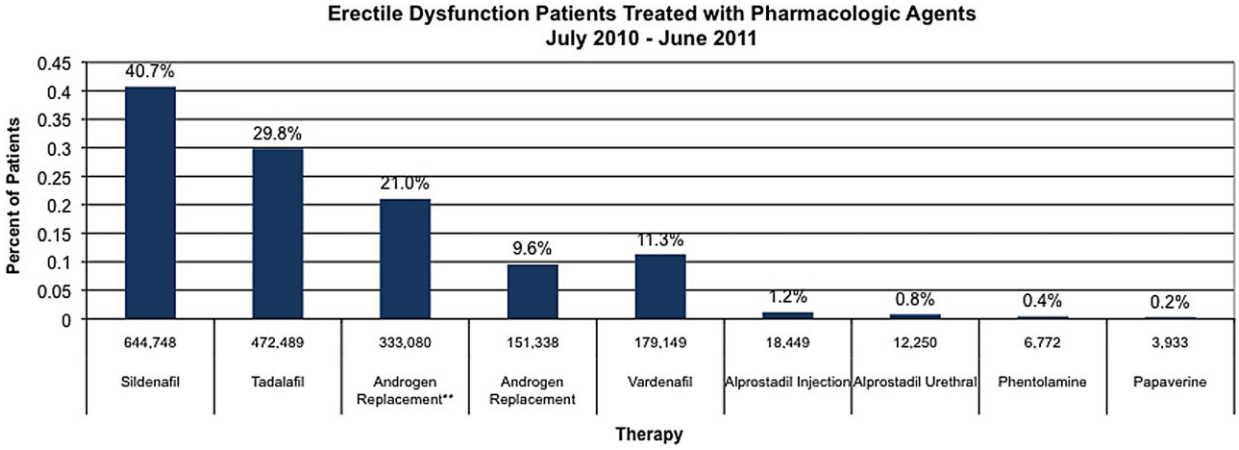

Figure 1 Pharmacologic treatment of erectile dysfunction (ED) in study cohort.
Analysis of the frequency of ED medical therapies among "treated" men demonstrates that the phosphodiesterase type 5 inhibitor (PDE5i) class is prescribed at a significantly ($P < 0.0001$) greater frequency compared with all other ED therapies.
**Co-diagnosis of hypogonadism.

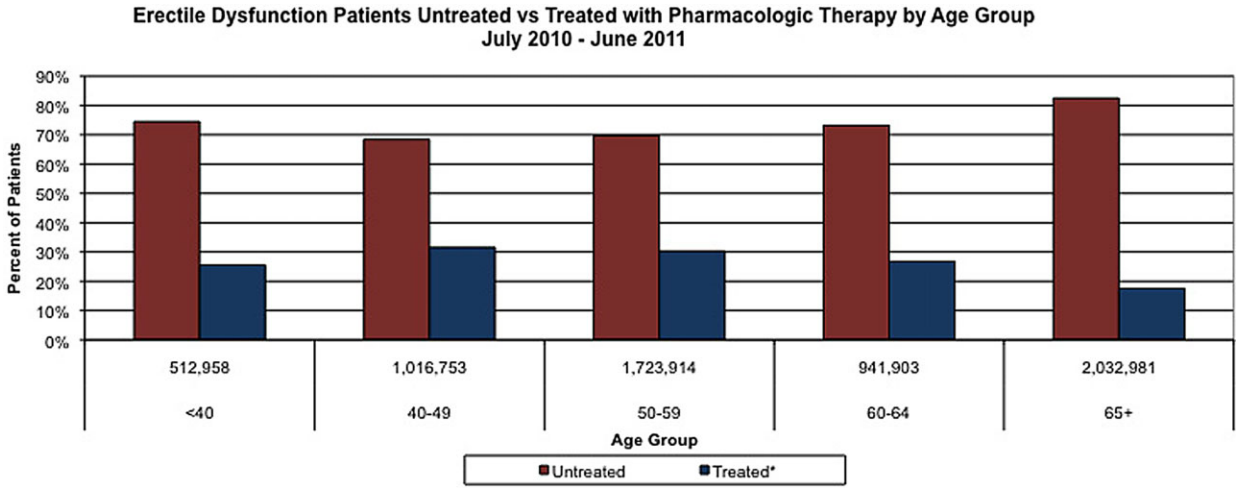

Figure 2 Erectile dysfunction treatment rates by age group.
There was not an increased frequency of ED diagnosis as a function of age.

(see Materials and Methods section). There was a significant increase in frequency of ED with the number of comorbidities ($P < 0.001$, Armitage chi square analysis test for trend). Specifically, among the total population of men with ED, 13.8%, 22.0%, 22.6%, and 41.6% had 0, 1, 2, and ≥3 comorbidities, respectively (Figure 4). There was no significant difference in treatment frequency based upon the number of comorbidities as ~25% of men were treated in all comorbidity groups. However, there were significant differences in ED treatment frequency based upon individual comorbidity type (Figure 5). For example, only 15% of men with ED and prostate cancer filled a prescription during the study period. In contrast, a significantly ($P < 0.0001$) greater proportion of men filled a prescription for an ED medical therapy with a co-diagnosis of hypogonadism (51%, relative risk [RR] = 3.40). The frequency of treatment for other comorbidities and RR of treatment in comparison with prostate cancer is shown in Table 1.

In our cohort, 2,348,960 (38%) were diagnosed by urologists. This was the largest proportion compared with any other specialty. General/family practice and internal medicine/geriatrics diagnosed 2,020,731 (32%) and 1,009,005 (16%) patients, respectively. Physician specialty was also associated

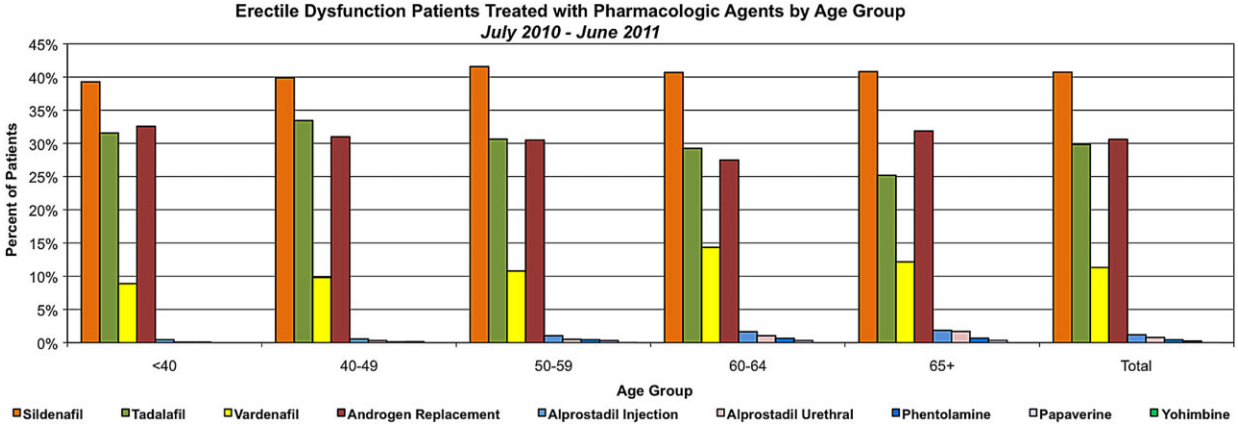

Figure 3 Pharmacologic treatment types by age group.
Evaluation of medical therapy as a function of age group demonstrates that the phosphodiesterase type 5 inhibitors (PDE5is) were the most commonly filled prescription in every age group. While the overall proportion of men treated with injectable therapies was infrequent, their frequency generally increased with advancing age.

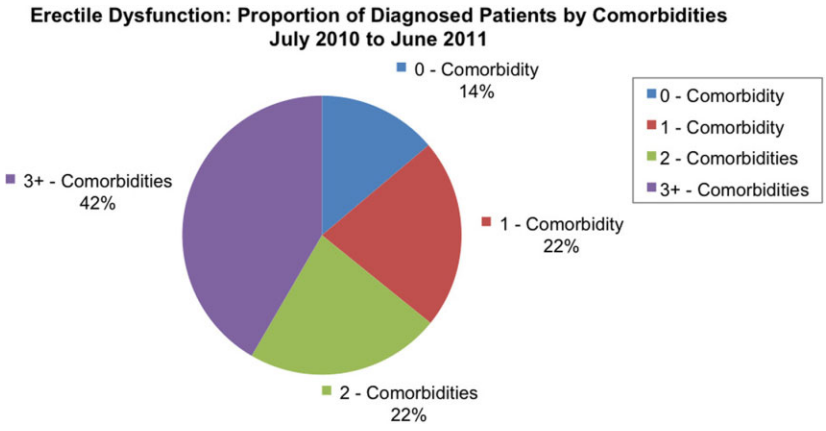

Figure 4 Comorbidity effect on erectile dysfunction (ED) diagnosis. There was a significant increase in frequency of ED as the number of comorbidities increased. There was no significant difference in treatment frequency based upon the number of co-\morbidities as approximately 25% of men were treated in all comorbidity groups.

with the frequency of ED treatments (Figure 6). Among physicians most likely to see patients with ED, the percentage of patients treated for their ED ranged from as low as 18% (cardiology) to as high as 29% (general/family practice). Although urologists were the most likely to diagnose ED, they were not the most likely to have a prescription filled for ED as only 23% of men with ED had such a prescription filled during the study period.

Discussion

Many studies have documented the prevalence of ED and its association with advanced age and specific comorbidities [2,4,8]. However, to our knowledge, this is the first study to report the frequency of associated ED medical therapies in a relatively large patient population. It has previously been assumed that a significant percentage of men suffer from ED and remain undiagnosed unless specifically questioned about this problem. Putatively, the most common reason for underreporting of ED is patient embarrassment or decreased bother/severity [13]. However, it has been shown that once the topic is initiated, patients become willing to discuss their potency issues. Despite the high prevalence of ED and its associated impact on QoL, this disease largely remains medically undertreated. This point is well documented herein as only 25.4% of the men diagnosed with ED were treated with medications. The potential reasons why >75% of diagnosed men do not receive medical therapy include a lack of bother, a proclivity to diagnose mild ED, lack of partner or other partner-related issues, patients erroneously accepting ED as a normal part of aging or an expected state attributed to the accumulation of relevant comorbidities, medication costs, patients who are in the midst of ED evaluation, those who failed a previous ED treatment and no longer pursue therapy, and the

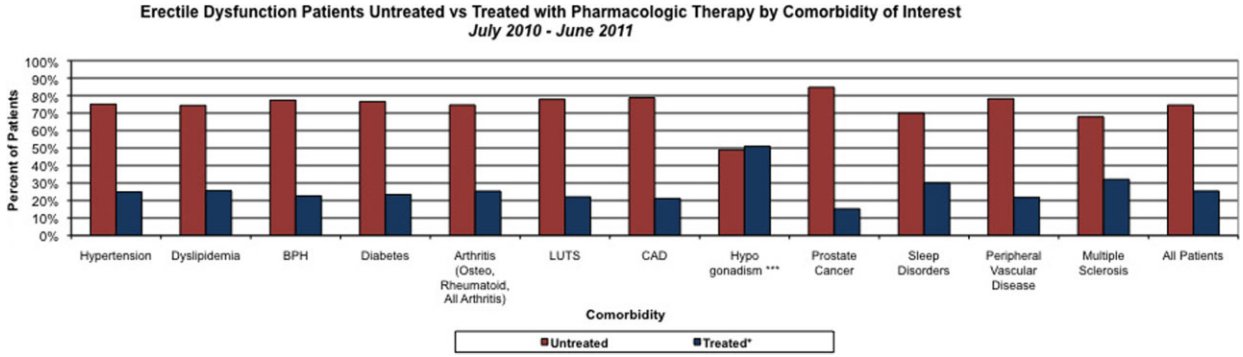

Figure 5 Pharmacologic treatment rates of erectile dysfunction (ED) patients with various comorbidities. There were significant differences in ED treatment frequency based upon individual comorbidity type. Only 15% of men with ED and prostate cancer filled a prescription during the study period. Noteworthy was a significantly greater proportion of men filling a prescription for an ED medical therapy with a co-diagnosis of hypogonadism. BPH = benign prostatic hyperplasia; CAD = coronary artery disease; LUTS = lower urinary tract symptom. *Those given a prescription for treatment, ***Number of patients with hypogonadism and treated with androgen replacement therapy is 333,080.

Table 1 Treatment rates and likelihood of treatment by specific comorbidity

Frequencies of medical intervention by comorbidity		
Comorbidity	% treated	Relative likelihood of treatment
Prostate cancer	15	—
BPH	23	1.53
LUTS	22	1.46
Hypertension	25	1.67
Dyslipidemia	26	1.73
Diabetes	23	1.53
CAD	21	1.40
Arthritis	25	1.67
Hypogonadism	51	3.40
Sleep disorders	30	2.00
Peripheral vascular disease	22	1.46
Multiple sclerosis	32	2.13

There was marked variation in the likelihood that a patient with a particular comorbidity is treated for ED. Note the low probability that a man diagnosed with prostate cancer is treated vs. one with multiple sclerosis
BPH = benign prostatic hyperplasia; CAD = coronary artery disease; LUTS = lower urinary tract symptom

prescribing decisions of treating physicians. Because our analysis only covered a single year in time, there could be patients who continue to carry a diagnosis of ED but have failed ED therapy in the past and are not currently being treated. Our analysis did not address vacuum erection device therapy or ED surgery although these treatments comprise only a small portion of men treated for ED. There were 22,420 penile prostheses placed in the United States in 2009 [14]. Even allowing for a small increase in that number for our time period, including those treatments in our analysis, would only affect the overall treatment rate by a few percent.

PDE5is are considered to be the first-line therapies for the treatment of ED [8,9,15,16]. Several randomized controlled trials (RCTs) have demonstrated the efficacy and relatively low side effect profile of this class of medications. A meta-analysis of 14 RCTs involving 2,283 men reported that sildenafil (all doses) significantly increased the proportion of patients who had at least one episode of successful intercourse compared with placebo (83% with sildenafil vs. 45% with placebo; RR 1.8, 95% confidence interval 1.7–1.9) [16]. Based on national and state retail prescription data compiled by IMS Health, the present study shows that the PDE5i class medications dominates the market with approximately 75% of all prescriptions for ED being written for this class. Based on this dataset, when medical therapy is utilized for ED (n = 1,583,003), 75.2% (n = 1,189,990) are placed on a PDE5i. While the present study shows that the PDE5i class use is dominated by sildenafil (40.7%) compared with tadalafil (29.9%) and vardenafil (11.3%), it is important to note that there is no compelling data to support the superiority of one PDE5i over another [8]. It has been shown that many injectable therapies can be successfully used to treat ED that is refractory to PDE5i [17,18]. However, while efficacious, the present results show that the second-line therapies are used by a substantially smaller portion of the men with ED. When initiated, these therapies tend to be used in older men.

Despite common uncertainties associated with the diagnosis and clinical implications of a low testosterone level, ART is commonly used for men with ED [19]. In a meta-analysis of 16 studies, improvement in ED was significantly more common in hypogonadal men treated with testosterone than with placebo (57.0% vs. 16.7%) [19]. Among nine prior studies that included data on the

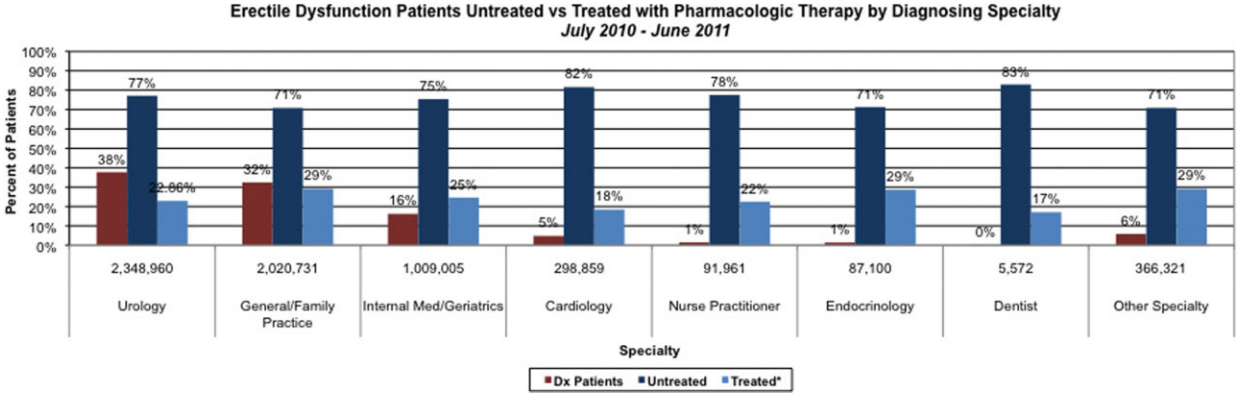

Figure 6 Diagnosis and pharmacologic therapy in patients with erectile dysfunction (ED) by medical specialty. There was great variability in the number of patients diagnosed vs. treated for ED based on specialty focus of the health professional. Dx = diagnosed.

etiology of ED, the response rate was significantly higher in men with primary testicular failure (64%) compared with those with a secondary cause of ED (44%) [19]. The current results suggest that almost 25% of men with ED and hypogonadism are treated with ART. Another 9.6% of men are treated with androgen replacement but do not have a diagnosis of hypogonadism. Reasons for this latter discrepancy may include coding errors, previous coding maneuvers outside the evaluation period, or perhaps health care provider error. It is important to note that testosterone is not a treatment for eugonadal men with ED but may be beneficial in men with confirmed hypogonadism. This was one of five treatments or tests to question shown in the American Urological Association's contribution to the Choosing Wisely campaign (http://www.auanet.org/advnews/press_releases/article.cfm?articleNo=285). In addition, ART appears to be most pronounced in older (≥65 years) and younger men (<40 years). It should be noted that this trend in the younger age population may be concerning, as there is some debate about the requirement of ART in this population [10].

Although it is well-known that the frequency of ED increases with advancing age, our results demonstrate that treatment rates do not follow the same trend. The lack of therapy in older men may reflect the fact that the percentage of men motivated to receive treatment remains constant. However, it may also reflect the fact that other comorbidities that increase with age may limit treatment effectiveness or a high rate of prior therapy failures. Interestingly, young men also are undertreated. Reasons for this may be related to severity of ED or patient comfortability filling a prescription.

The present study demonstrates that a diverse group of comorbidities substantially influences the risk of ED. We found that the prevalence of ED increases with the number of documented comorbidities. Specifically, there was a statistically significant association between the ED and the number of comorbidities (0 comorbidities was 14% vs. 42% with 3 + comorbidities). This fits with the current understanding that many diseases affect erectile function [4–8]. It is interesting that despite this relationship, the treatment frequency does not correspondingly increase with the comorbidity count. This is surprising because as one adds comorbid conditions, there is both a disease effect, which we demonstrated, and a mounting medication effect that could affect ED and treatment. This may reflect the fact that patients with increased comorbidities cannot receive therapy because of their potential side effects or cost [13,20,21]. Further study is this area is warranted.

We documented that patients are much more likely to receive ED therapy with certain comorbidities (e.g., hypogonadism, sleep disorders). However, a significantly lower percentage of patients with other comorbid diseases (e.g., prostate cancer) fail to receive ED treatment. It is possible that many patients with these comorbid conditions relate to a prior failure to respond to medical therapies.

This study is not without limitations. First, analysis of patients from the IMS Health dataset is limited to diagnostic and therapeutic treatment patterns within a large cohort of privately insured individuals. Patient populations, such as those insured by Medicare/Tricare and those without health insurance, should similarly be examined. Additionally, diagnosis and treatment are recorded using standardized ICD-9 codes, which do not stratify patients according to the cause of ED. The etiology of ED in a given patient, whether iatrogenic (e.g., postsurgery or radiation) or pathophysiologic (e.g., atherosclerotic), can greatly affect the response to a particular treatment. We were not able to assess those who had radical pelvic surgery as there is not a specific code. Further, ICD-9 coding does not take into account previous treatment or treatment efficacy. Based on this dataset, it is unclear whether patients have tried additional treatments for ED within or across classes of medications, what the efficacy or duration of each treatment is, or what the course of the disease is. We also do not know who was given a prescription but did not fill it for various reasons. We also were unable to assess if patients carried a diagnosis of ED into the studied time but were treated outside of our time frame of inquiry. An additional potential limitation is that our study does not address psychogenic treatment for ED. These data are based on administrative claims data using ICD-9 codes for organic ED. This by definition would exclude those cases that are coded correctly as psychogenic ED, and so inferences about such ED etiologies are beyond the focus of the current work.

Conclusion

The current study shows that in a large population of men diagnosed with ED over a period of 1 year, the majority are undertreated, regardless of patient age or number of associated comorbidities. By far, the most common medical intervention for ED is

the use of PDE5is, followed by testosterone replacement and injectable intracavernosal or transurethral therapies. Further study into treatment history, etiology of undertreatment, and individual efficacy is required. Based on these data, additional benefit may be gained by increasing education of patients and physicians about the availability and efficacy of medical treatments for ED.

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Conflict of Interest: Kevin T. McVary is a meeting participant/lecturer for GSK; received honorarium from Allergan, Lilly/ICOS, NxThera, and Watson Pharmaceuticals; is a principal investigator for Allergan, Lilly/ICOS, Neotract, and NIDDK; is a consultant or advisor for Allergan, Lilly/ICOS, NxThera, Watson Pharmaceuticals, and Neotract; and conducted a scientific study or trial for Allergan, Lilly/ICOS, and NxThera. All other authors report no conflicts of interest.

Statement of Authorship

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(c) Analysis and Interpretation of Data
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(a) Drafting the Article
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(b) Revising It for Intellectual Content
Kevin T. McVary; Brian T. Helfand; Luke R. Frederick

Category 3

(a) Final Approval of the Completed Article
Kevin T. McVary; Brian T. Helfand; Luke R. Frederick

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