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Quality of Life and Sexual Function Benefits Effects of Long-Term Testosterone Treatment: Longitudinal Results from the Registry of Hypogonadism (RHYME)

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Abstract

Background: The benefit and risks of long-term testosterone administration has been a topic of much scientific and regulatory interest in recent years.

Aim: To assess long-term quality of life (QOL) and sexual function benefits of testosterone replacement therapy (TRT) prospectively in a diverse, multi-national cohort of hypogonadal men.

Methods: A multi-national patient registry was used to assess long-term changes associated with TRT in middle-aged and older men with HG. Comprehensive evaluations were conducted at 6, 12, 24, and 36 months after enrollment into the registry.

Outcomes: Quality of life and sexual function were evaluated by validated measures, including the Aging Male Symptom (AMS) Scale and International Index of Erectile Function (IIEF).

Results: A total of 999 previously untreated men with HG were enrolled at 25 European centers, 750 of whom received TRT at one or more visits during the period of observation. Patients on TRT reported showed rapid and sustained improvements in QOL, with fewer sexual, psychological and somatic symptoms. Modest improvements in QOL and sexual function, including erectile function, were also noted in RHYME patients not on TRT, although treated patients showed consistently greater benefit over time in all symptom domains, compared to untreated patients. Total AMS scores for patients on TRT were 32.8 (CI: 31.3-34.4) compared to 36.6 (CI: 34.8-38.5) for untreated patients ($p<.001$). Small, but significant improvements in IIEF scores over time were noted also with TRT. Approximately 25% of both treated and untreated men also used PDE-5 inhibitors (PDE-5i's), with notable differences in the frequency of PDE-5i prescription use according to physician specialty and geographic site location.

Clinical Implications: TRT-related benefits in quality of life and sexual function are maintained well for up to 36 months following initiation of treatment.

Strengths and Limitations: The major strengths are the large, diverse patient population being treated in multi-disciplinary clinical settings. The major limitation is the frequency of switching from one formulation to another.

Conclusion: Overall, we confirmed the broad and sustained benefits of TRT across major QOL dimensions, including sexual, somatic and psychological health, which were sustained over 36 months in our treatment cohort.

KEY WORDS: Testosterone replacement therapy, hypogonadism, sexual function, quality of life, PDE-5 inhibitors

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Introduction

The decline in serum testosterone associated with hypogonadism (HG) in men is typically accompanied by a noticeable loss of sexual desire or libido, decreasing sexual performance and adverse changes in mood, energy and subjective well-being [1-8]. These common, bothersome symptoms are the primary reason that increasing numbers of men around the world currently seek testosterone replacement therapy (TRT), in addition to other potential clinical benefits of treatment on musculo-skeletal and metabolic functions [9-12].

The role of hypogonadism in reduced quality of life (QOL) and loss of sexual interest or activity in men is well established. In the European Male Aging Study (EMAS) [13], well-defined sexual symptoms, including loss of sexual desire, decreased frequency of sexual thoughts, and absence of spontaneous or nocturnal erections, were associated with lower levels of testosterone (T) in a large, population of 3300 men in 8 European countries. Sexual symptoms were similarly associated with below normal T levels in the Boston Area Community Health (BACH) study, a large, population-based survey of 1389 US men [1]. Nearly 10% of men over 45 in the BACH sample had testosterone deficiency and low desire, and 15% had low T and erectile dysfunction (ED). An additional 14% had depressed mood symptoms and 15% had loss of musculo-skeletal strength or onset of frailty.

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around the world currently seek testosterone replacement therapy (TRT), in addition to being an important potential clinical benefit of treatment [9-12].

Findings from two recent large, randomized placebo-controlled trials confirmed significant benefits in restoration of sexual desire, improved well-being and other QOL benefits of TRT. Significant improvements in sexual function and vitality were reported in a large, multicenter 12-week trial of daily, topical TRT in hypogonadal men aged 55 on average [14], and moderate improvements in sexual activity and desire were reported following 52-weeks of TRT in elderly hypogonadal men in the NIH-funded, T-Trial [15, 16]. In the latter study, a slight decline in sexual function was noted during the final month of treatment [16].

The effects of long-term maintenance TRT on sexual function and QOL has not been adequately evaluated in large, well-controlled studies. Persistent effects of TRT on sexual function and QOL were reported recently in a single-center uncontrolled study of 261 patients with late onset hypogonadism (LOH), all of whom received testosterone undecanoate (TU) injections for up to 5 years [17]. Clinically significant improvements and sustained benefits of TRT were noted in this study across multiple domains of sexual function and QOL, which were apparent in the first three months of treatment. These benefits persisted across all QOL domains over the average 5-year period of follow up in this study.

The Registry of Hypogonadism in Men (RHYME) is a prospective, multi-national patient registry including a broad age-range of men with diagnosed hypogonadism, none of whom had prior treatment with testosterone, and all patients received extensive medical and psychosocial evaluation at the time of enrollment [18]. The RHYME study was designed primarily to evaluate safety outcomes, including

prostate safety and cardiovascular events and mortality; these results have been reported elsewhere [19, 20]. We now present the secondary outcomes of RHYME on sexual function and QOL symptoms which were assessed by means of validated and widely used symptom scales and were analyzed as secondary outcomes [18]. The current paper presents longitudinal data on sexual function and QOL benefits of TRT in RHYME.

Methods

RHYME is a prospective, multi-national patient registry of treated and untreated men with HG implemented in 25 sites across 6 European countries (Germany, Italy, Netherlands, Spain, Sweden, and the United Kingdom). Countries were selected to include both northern and southern European countries, in addition to those European countries with established reimbursement policies and sufficient numbers of andrology or urology practices for effective management of patients. Clinical site investigators included approximately equal number of urologists (N=13) and endocrinologists or general physicians (N=12), and were selected based on their experience and familiarity with HG management guidelines and adequate facilities and staff to participate in a large, multi-national patient registry.

Eligibility criteria for registry participation included men aged 18 years and older with a diagnosis of HG, confirmed by low testosterone on at least two occasions. The determination of low testosterone was made by the clinical site using local laboratory, total testosterone values in most cases. Central laboratory assays were made available only to the data center (NERI) and could not be accessed by site physicians or study coordinators due to the non-interventional nature and observational design of the study [18]. Central laboratory assays included total testosterone by means of liquid

chromatography tandem mass spectrometry (LC-MS) ; sex hormone binding globulin (SHBG); luteinizing hormone (LH); prostate specific antigen (PSA).

Patients were excluded if they had received prior treatment of any testosterone products or a past history of breast or prostate cancer, high-grade prostatic intraepithelial neoplasia, radical prostatectomy or life expectancy shorter than 24 months as judged by the clinical site investigator. Patients with major psychiatric disorders, drug or alcohol abuse, or gender dysphoria were also excluded. All eligible patients were enrolled consecutively, which reduced selection bias. Once enrolled, patients and physicians made a conjoint decision to initiate TRT; overall 80% of patients chose to initiate treatment. Patients were not required to record their reasons for choosing or declining TRT.

Each patient enrolled was scheduled for at least four (4) and up to five (5) assessments over a minimum of 2 years starting at baseline and then the following 3-6 months, 12 months, 24 months, and 36 months. Baseline and follow-up data collection included complete medical history, physical examination, blood sampling, and patient questionnaires (Figure 1). Data were collected through abstraction of medical records and a self-administered questionnaire designed to obtain information on demographic characteristics, lifestyle factors (e.g., smoking, physical activity), and other health information. Quality of life was monitored at repeated visits by means of the Aging Male Symptom (AMS) scale, a validated 17-item, quality of life measure which has been used in previous studies of androgen effects in aging men [21, 22]. The AMS sexual symptom scale includes patient complaints of low desire, diminished potency and erection difficulties, in addition to decreased beard growth. The AMS psychological domain covers symptoms of depressed mood, negative attitude and irritability, while the somatic scale includes symptoms of excessive sweating, sleep disturbance and lack of physical

energy. The somatic scale comprises 7 items, while the psychological and sexual scales are comprised of 5 items each [21, 22]. Sub-scale scores were computed independently for the Sexual, Psychological and Somatic Subscales of the AMS [21] and the Total AMS Score for overall QOL impact [21, 23]. The International Index of Erectile Function (IIEF), a multi-dimensional scale of male sexual function, was administered at successive study visits, and sub-scale scores computed for two primary domains of erectile function (EF) and sexual desire (SD) [23]. Lower urinary tract symptoms (LUTS) were monitored at every visit by means of the International Prostate Symptom Score (IPSS); results for this measure are reported elsewhere [19].

Additional diagnostic tests or procedures, including prostate biopsy or ultrasound tests, were requested by the treating physician in consultation with the patient. This clinical decision-making was intended to reflect real-world clinical practice in order to increase generalizability of the RHYME findings, being consistent with the non-interventional nature of a registry design. A complete description of the RHYME trial design and methodology has been published previously [18].

The disposition of the RHYME cohort according to TRT status is shown in Figure 2. Of the 1,006 patients enrolled, 7 were found ineligible, resulting in an analytic cohort of 999 patients. A total of 71 patients were terminated during the study, resulting in a patient retention rate of 92.9% over 3 years of follow-up. Reasons for early termination included death, loss to follow-up and withdrawal of consent. Approximately 23,900 person-months were accrued, which represented 99.6% of the targeted follow-up period. All patients provided written informed consent prior to enrollment. Registry protocols were approved by local Ethics Committees (EC) at each clinical site.

Statistical Analyses

Descriptive statistics, including mean or median, standard deviation (SD) and frequency measures were used to characterize the pre-treatment characteristics of our sample, and to assess baseline differences between those who went on to be treated with testosterone versus those who were not subsequently treated due to patient or physician choice of treatment options. To ensure maximum opportunity for capturing effects of exposure to TRT, we considered participants to be in the "treated" group if treatment was initiated at any follow up visit. Conversely, untreated subjects did not receive TRT at any time during the period of study.

Longitudinal mixed model analyses evaluated changes in quality of life and sexual function outcomes. These analyses modeled outcomes according to the effects of TRT assignment and time in treatment, in addition to interaction effects across time. Testosterone therapy was treated as time-varying in the longitudinal model. Using baseline measured covariates, multivariate modeling was performed to control for confounders. All covariates were entered into single multivariate models predicting each outcome. Those with a p-value of ≤ 0.2 in each model were selected as final covariates for the fully adjusted model. Covariates considered in analyses included: age, country, baseline comorbidity, modified Charlson Index score, duration of HG prior to treatment, BMI, prior urologic or prostate diseases, lower urinary tract symptoms (LUTS), smoking, laboratory measures (cholesterol, TT, SHGB, LH, PSA), and certain medications [for hypertension, diabetes, lipid-lowering, erectile dysfunction (ED), psychiatric disorders, and benign prostate hyperplasia (BPH)]. SAS 9.3 was used for statistical analyses.

Results

A. Cohort Characteristics: Treated vs. Untreated Patients

Baseline characteristics of RHYME participants are shown in Table 1. The mean age of the cohort at baseline is 59.1±10.5 years old and mean baseline TT was 9.5 ± 0.5 mol/L. Of the 999 patients enrolled with clinically-diagnosed hypogonadism, 750 (75%) received at least one prescription for TRT ("treated") and 249 (25%) did not receive TRT in any form ("untreated"). TRT-treated and untreated men were not different in age, type of hypogonadism or other sociodemographic characteristics at baseline. Cardiometabolic profiles were also similar in the two groups prior to TRT. Men who subsequently received TRT were more symptomatic at baseline (Mean AMS Score = 35.9 ± 11.4 vs 41.4 ± 13.1 for TRT treated vs untreated men). Treated men also had higher rates of ED prior to treatment compared to untreated men (64.4% vs 56.2%), and the rate of other urologic diseases, including BPH and Peyronie's disease, were higher in the TRT group (76.4% vs 67.9%). Gynecomastia was noted in 11.1% of men in the TRT group prior to treatment compared to 6.9% in the untreated group, although similar rates were observed during the follow up period (6.6% for treated vs 7.1% for untreated men). None of the participants had received prior TRT, as required by the RHYME eligibility criteria, although frequent use of concomitant medications was observed, including antihypertensives, antidiabetics and lipid-lowering medications (Table 1).

B. Treatment Effects on QOL and Sexual Function

(i) AMS Total Symptom Score

Changes over time in total AMS symptom scores for treated and untreated men are shown in Figure 3. Despite higher baseline scores in the treated group, a reduction of approximately 7 points (11%) was maintained during the follow up

period for men on TRT, compared with 4.5 points (6%) for the untreated men (Figure 3). For men who received T injections or prescriptions on at least half or more of their study visits (N=566), the average improvement in quality of life scores was even greater to ~8.0 points. Among consistently treated men, those who began treatment with an injectable formulation showed a trend towards slightly greater symptom reduction over time (31.9 vs. 33.0), despite higher initial scores for the injectable group (41.0 vs 37.6). Initial treatment with topical fomulations showed a similar trend, though less pronounced.

Statistical modeling with longitudinal adjustment for covariates demonstrated significant treatment effects over time, with significantly less overall symptom benefit in the untreated group; men receiving TRT showed consistently greater symptom reduction (lower score = fewer symptoms), beginning at 3-6 months and continuing for up to 3 years. This difference in benefit between treated and untreated patients was maintained over time, despite higher baseline or pre-treatment symptom levels in patients subsequently assigned to TRT.

Both the treatment effect (TRT vs non-TRT) and treatment X time interaction were significant ($p<.001$) in multivariate, longitudinal analyses, as shown in Table 2. AMS scores were consistently lower in the TRT compared to the non-TRT condition, and this difference was maintained throughout the follow up period (Figure 3). Treatment effects were similar for men with an initial diagnosis of secondary hypogonadism (N=616) compared to the overall cohort (N=999).

(ii) AMS Sexual Symptoms

Sexual symptoms were similarly improved in both groups; however, patients receiving TRT again showed consistently greater benefit over time compared to

untreated men (Figure 4). Sexual symptom scores were reduced from the moderate to the mild range in both groups, although a significant benefit in favor of the treated group was observed (p<.001). Both treatment effect and treatment X time interactions were highly significant (P<.001), as shown in Table 2. A consistent difference in favor of TRT-treated men was observed throughout the 3-year follow up period (Figure 4). Similar trends were observed also for men with an initial diagnosis of secondary hypogonadism and for consistent compared to inconsistent TRT users. Sustained reductions in sexual symptoms were similarly noted for those who initiated therapy on injectable compared to topical agents.

(iii) AMS Psychological Symptoms Subscale

Significant improvements in psychological symptoms (e.g., mood, energy) were similarly observed over time in both groups (p<.001), although the treated group showed significantly greater improvement overall in the adjusted model compared to the untreated men (p<.001) (Figure 5). Average scores for psychological symptoms declined from 9.4 $\pm$ 1.2 to 8.1 $\pm$ 0.6 for the treated group, and from 9.1 $\pm$ 1.1 to 7.8 $\pm$ 0.9 for the untreated group. A significant interaction of treatment over time was again observed (p<.007) (Table 2).

(iv) AMS Somatic Symptoms Subscale

A significant decrease was similarly observed in the somatic symptom scores for treated vs. untreated men in the adjusted models and a marked decrease over time was seen in both treated and untreated patients (Figure 6). Both groups declined from the moderate to the mild somatic symptom range, with a change of 2.2 points on average in the treated group compared to 1 point improvement in the untreated group (Figure 6). A statistically significant interaction of treatment by time was also seen

for this measure (i.e., fewer somatic symptoms in the treated group over time). Similar to the psychological symptoms score, adjusted means show somatic symptoms to be consistently improved in treated compared to untreated patients, despite higher baseline scores in the treated group. Of note, a relatively slight increase in somatic symptoms was observed in the untreated group during the last year of follow up, compared to treated men who maintained their improvement over time (Figure 6).

(v) IIEF Erectile Function Domain

EF domain scores showed similar trends in favor of TRT ($p<.001$), after multivariate analysis accounting for age, BMI, concomitant medications and other covariates (Figure 7). Erectile function increased approximately 0.1% per month in the treated group, a small but significant effect on adjusted means ($p<0.001$; See Table 2). A borderline statistically significant interaction of treatment and time was noted for erectile function domain scores, with a trend towards greater improvement in erectile function in men on TRT over time. Overall, mean domain scores for the erectile function scale were 18.9 in treated men vs. 17.0 in untreated men (Table 2), despite lower initial EF scores in patients subsequently receiving TRT (Figure 7).

(vi) IIEF Sexual Desire Domain

A similar pattern of positive response to TRT was seen in results for sexual desire scores, as shown by the Sexual Desire domain scores from the IIEF scale (Figure 8). Again, treated patients showed a significant improvement on this measure during the first 6 months of TRT, which was sustained for the following 24-36 months. Significant differences, although small magnitude (10% in treated men; 7% in untreated men) were observed, although the relative improvement during treatment

for the TRT group is highlighted by near-identical mean sexual desire scores in the two groups prior to treatment (Figure 8).

C. Use of Phosphodiesterase Type 5 Inhibitors (PDE-5is)

Approximately 25% of men in both groups were regular users of PDE-5is at enrollment and the majority continued to use PDE-5is during the course of RHYME. Significant variations in the frequency of PDE-5i use were associated primarily with treating physician specialty (Chi-Square=50.8, $p<0.0001$) and clinical site location (Chi-Square=65.6, $p<0.0001$). As shown in Figures 9a and 9b, PDE-5i's were prescribed more frequently by urologists (35.9%) compared to endocrinologists or general practitioners (16.1%). The highest percentage of PDE-5i prescriptions were administered to RHYME patients in Spain (ES) (44.2%), which also had a high representation of urologic sites (4/5).

Discussion

The results of this prospective, multi-national HG clinical outcomes registry provide further evidence of sustained and consistent benefits of TRT in improving long-term quality of life and sexual function in a large, diverse cohort of hypogonadal men (18); findings which are in keeping with outcomes reported in recent randomized controlled trials [14, 15, 16]. The consistency of these effects across trials and studies, treatment groups and different outcome measures is robust and compelling. In particular, sexual desire or activity measures in these studies showed the same significant, albeit relatively modest magnitude of change with treatment. Erectile function was improved, but only marginally by TRT, after controlling for the effects of concomitant medications and comorbidities. Other, non-sexual quality of life outcomes showed greater degrees of

improvement, despite differences in the types of TRT administered and study populations.

In general, RHYME participants who received TRT at one or more treatment visits showed consistent, sustained symptom improvement compared to untreated patients over the course of RHYME. These benefits and improvements in psychological, sexual and somatic symptoms were evident as early as 3-6 months following initiation of treatment, and persisted over the course of 36 months of follow-up. More modest symptom improvements were also noted in RHYME patients not receiving TRT, which may have been due to non-specific effects of scheduled contact with medical staff at participating sites or more specific effects of active management of concomitant medical conditions (approximately 25% were diabetic; about 50% were hypertensive) and the use of concomitant medications (25% were prescribed PDE-5i's; 20% had alpha blockers), or recommended lifestyle changes (e.g., reduced stress, weight loss). Despite similarities in health status and medical management across the two patient groups, however, patients on TRT showed consistently greater symptom improvement on all QOL component measures. These symptom benefits persisted over a strictly monitored, 36 month follow up period.

It should be noted that treated patients were more symptomatic and had a higher prevalence of ED prior to treatment, on average, and were more likely to have concomitant urologic or psychiatric conditions, infertility or past prostate biopsies. It is unclear what effect, if any, these concomitant conditions or past medical history may have had on the outcome of TRT, although the benefits in symptom improvement were clearly evident despite these baseline differences. Treated patients were slightly more overweight on average prior to treatment, although this difference failed to reach

statistical significance. Differences between patients treated with injectable TRT and those receiving topical formulations also failed to reach statistical significance in adjusted models.

Large and sustained QOL benefits have been reported recently in a single center HG treatment registry by Almehmadi et al [17] using the same symptom measures (AMS, IIEF, IPSS) as those used in RHYME [18]. Our results are broadly similar and showed benefits similar to those reported in this long-term (i.e., 5-year) observational study of long-acting, TU injection therapy in 261 patients with adult-onset hypogonadism (AOH). Patients in the Almehmadi et al study [17], were more symptomatic prior to TRT than RHYME patients [18], with Total AMS Symptom Scores >50 prior to treatment, which improved by 20+ points over 5 years of TU injections. Moreover, these effects were found to be reversible when TRT was withdrawn for a period of approximately 18 months, and then to largely recover when TRT was reinstated. [24, 25]

In contrast, in our RHYME cohort, mean AMS total scores were <40 prior to treatment (i.e., patients were less symptomatic), and scores improved by approximately 20-25% of baseline values of both AMS Total and Sexual Symptoms Sub-Scale scores of the AMS measure, in addition to sub-scale scores on the SD domain of the IIEF. Similar thresholds of benefit have been established for voiding and male sexual disorders [26, 27]. Moreover, our results were consistent across outcome measurement domains and individual measures, although the magnitude of change associated with TRT in RHYME was less pronounced than the 50% level of improvement reported by Almehmadi study [17]. The higher dysfunctional baseline scores in that study, extended duration of treatment (5 years vs 2-3 years) and highly consistent application of TRT with scheduled administration of long-acting TU injections in the physician's office giving 100%

compliance in the Almehmadi study [17] are all likely factors accounting for the greater degree of symptom benefit observed in that study compared to ours. In RHYME, a broad range of oral, injectable and topical TRT formulations were administered for different time periods and switching between formulations occurred. For these reasons, we were not able to correlate individual treatment benefits to specific formulations of TRT in RHYME.

Despite a variety of TRT formulations and dosages, and switching between formulations, the present study was able to confirm the broad and sustained benefits of TRT across major QOL dimensions, including sexual, somatic and psychological health, which were maintained over 36 months in our treatment cohort. Of note, the most substantial symptom benefit was observed in the somatic symptom domain, which includes 7 somatic complaints related to HG, such as excessive sweating, disturbed sleep and physical weakness. Modest, sustained improvements in LUTS were seen also in patients on TRT in RHYME, as reported elsewhere. [19] We could not show a statistical advantage for the injectable compared to topical formulations of TRT on QOL outcomes, although treatment disconintuations, switching from one TRT formulation or dose to another, concomitant uncontrolled use of PDE-5i's, and other factors may have obscured differences between formulations or dosages. It should be noted that the study was not designed or powered to compare one form of TRT to another, but to evaluate the overall risks and benefits of TRT.

Erectile function scores showed improvements in the predicted direction, although the magnitude of improvement in erectile function was markedly less than reported by Almehmadi et al [17]. Patients with AOH in that study had average EF domain score improvements >10 points from baseline during the course of 5 years of treatment with

long-acting TU injections [17]. Significant, but more modest improvements of 4+ points in EF scores were seen during 2-3 years of mixed TRT therapy in RHYME.

The level of improvement in EF scores observed in RHYME, on the other hand, is similar to results reported recently from the 12-month, randomized NIH trial (T-Trials) of topical testosterone in hypogonadal men over 65 [15,16]. In this multi-center, randomized placebo-controlled trial, 12 months of topical TRT resulted in consistent, clinically meaningful improvements in sexual activity and desire, but less improvement in erectile function, as measured similarly by the EF Domain of the IIEF [23]. Less than 10% of patients in the Snyder et al trial received concomitant PDE-5's during the 12-month period of treatment compared to 25% of patients in RHYME, although the amount of improvement in EF scores was roughly similar across the two studies.

Other studies have reported similar QOL and sexual function benefits of TRT using alternative outcome measures. For example, significant QOL benefits of daily topical TRT were observed with 16 weeks of TRT administration in another recent double-blind, randomized trial [14]. Significant improvements in patients on topical TRT were observed on a new self-report measure of sex drive and energy (SAID), in addition to a validated new hypogonadal energy diary (HED) [14]. Based on changes in these novel measures, significant improvements in QOL and sexual function were observed following 16 weeks of topical TRT compared to placebo. It is not possible to compare the magnitude of effects in this study (14) directly with results from RHYME or other recent studies [17, 25] due to difference in design, duration of treatment and outcome measures used.

Nevertheless, the overall pattern and direction of effects is similar across all of the recent TRT trials and registries [14, 15, 17], despite the highly diverse patient

populations, including those with 'functional' (as opposed to classical/pathological) hypogonadism associated with multiple comorbidities and concomitant therapies, such as those in RHYME. Taken together, the present findings, together with those from other recent studies (14, 15, 17), strongly support the view that sustained and clinically important benefits in QOL (especially related to sexual and physical function) can be achieved by TRT in hypogonadal patient irrespective of the hypogonadal etiology and patient's age or health status.

Given the ongoing controversies regarding the overall risk/benefit of TRT [28-30], it is especially important to document meaningful benefits of TRT, as recommended by the Institute of Medicine's report on TRT in 2004 [31]. The RHYME study, unlike other hypogonadism registries or uncontrolled observational studies, provides data for comparison of TRT effects with outcomes for an untreated group at the same study sites, albeit without randomization or double blind controls. Most importantly, our data show consistent improvements across measures, over time and across treatment conditions in TRT-treated men compared to a similar group of patients treated without TRT. This adds substantial weight to the positive results from recent large-scale trials and registries showing clinically meaningful, sustained QOL benefits for men receiving TRT by means of topical or injection formulations. Further studies are needed to determine which patients are more or less likely to show sustained QOL benefits with TRT, and to examine systematically the use of combined therapy with PDE-5i's, anti-depressant agents or lifestyle changes. In the meantime, our findings provide strong support for clinicians who use TRT regularly to improve QOL and sexual function in middle-aged and older patients with HG.

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Baseline Characteristic	N	All Subjects Combined: Overall Cohort n (%) or mean ± SD	Treatment (TRT) Status: Untreated (n=249) n (%) or mean ± SD	Treatment (TRT) Status: Treated (n=750) n (%) or mean ± SD	p-value
Age	999	59.1 ± 10.5	59.7 ± 11.1	58.9 ± 10.3	0.30
Age Group	999				0.27
<60 yr		516 (51.7)	121 (48.6)	395 (52.7)	
≥60 yr		483 (48.4)	128 (51.4)	355 (47.3)	
Type of HG	751				0.26
Primary HG (LH≥7.6)		135 (18.0)	39 (20.7)	96 (17.1)	
Secondary HG (LH<7.6)		616 (82.0)	149 (79.3)	467 (83.0)	
BMI	989	30.0 ± 5.5	29.4 ± 5.1	30.2 ± 5.7	0.04
Mean (median) time between HG diagnosis and entry into registry (mo)	999	4.2 (0.4) ± 16.6	4.3 (0.7) ± 14.5	4.2 (0.3) ± 17.2	0.93
Past Surgeries/Therapy	999				
Orchiectomy		27 (2.7)	1 (0.4)	26 (3.5)	0.01
Orchidopexy		18 (1.8)	4 (1.6)	14 (1.9)	0.76
Pituitary surgery		28 (2.8)	5 (2.0)	23 (3.1)	0.36
Radiotherapy		17 (1.7)	3 (1.2)	14 (1.9)	0.46
HG symptoms at time of diagnosis	999				
Erectile dysfunction		622 (62.3)	140 (56.2)	482 (64.4)	0.02
Decreased desire for sex		116 (11.6)	26 (10.4)	90 (12.0)	0.49
Fatigue/weakness/decreased strength		100 (10.0)	36 (14.5)	64 (8.5)	0.01
Aging Males' Symptoms (AMS) Score	975	40.1 ± 13	35.9 ± 11.4	41.4 ± 13.1	<0.0001
Infertility		39 (3.9)	18 (7.2)	21 (2.8)	<0.01
Gynecomastia	979	98 (10.0)	17 (6.9)	81 (11.1)	0.06
Chronic diseases/comorbidities at baseline	999				
Urologic Disease*		742 (74.3)	169 (67.9)	573 (76.4)	0.01
Endocrine Disease		532 (53.3)	129 (51.8)	403 (53.7)	0.60
Cardiovascular Disorder		515 (51.6)	125 (50.2)	390 (52.1)	0.60
Pulmonary Disease		130 (13.0)	29 (11.6)	NA	-
Psychiatric Disease		151 (15.1)	24 (9.6)	127 (16.9)	0.01
Top 5 concomitant medications at baseline	999				
Anti-hypertensive medications		495 (49.5)	119 (47.8)	376 (50.1)	0.53
Lipid lowering medications		391 (39.1)	89 (35.7)	302 (40.3)	0.20
Anti-diabetes medications		257 (25.7)	65 (26.1)	192 (25.6)	0.88
Erectile dysfunction medications		253 (25.3)	60 (24.1)	193 (25.7)	0.62
Peptic ulcer medications		180 (18.0)	41 (16.5)	139 (18.5)	0.48
LUTS Severity (based on IPSS score)	980				0.87
None to mild (<8)		584 (59.6)	148 (61.7)	436 (58.9)	
Moderate (8-19)		308 (31.4)	73 (30.4)	235 (31.8)	
Severe (≥20)		88 (9.0)	19 (7.9)	69 (9.3)	
Erectile Dysfunction (based on IIEF score)	981				<0.01
None to mild (≥22)		343 (35.0)	104 (43.5)	239 (32.2)	
Moderate to severe (<22)		638 (65.0)	135 (56.5)	503 (67.8)	
Past prostate biopsies	999	37 (3.7)	18 (7.2)	19 (2.5)	<0.001
Past DRE	999	774 (77.5)	181 (73.0)	593 (79.1)	0.05
Abnormal result	774	195 (25.2)	57 (31.5)	138 (23.3)	0.03
Male kin with prostate cancer	987	56 (5.7)	18 (7.3)	38 (5.1)	0.19

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	Total AMS n=566			*AMS Sexual Symptoms* n=845			*AMS Psychological Symptoms* n=630			*AMS Somatic Symptoms* n=859			*IIEF Erectile Function Domain* n=671			*IIEF Sexual Desire Function* n=904		
Effect	**% change¥**	**CI∞**	**p-value**	**% change¥**	**CI∞**	**p-value**	**% change¥**	**CI∞**	**p-value**	**% change¥**	**CI∞**	**p-value**	**% change¥**	**CI∞**	**p-value**	**% change¥**	**CI∞**	**p-value**
TRT	-13.6	-15.6, -11.6	<0.001	-18.8	-20.9, -16.6	<0.001	-9.4	-12.0, -6.8	<0.001	-11.9	-14.0, -9.7	<0.001	2.5	1.8, 3.1	<0.001	0.9	0.8, 1.1	<0.001
Time	-0.4	-0.6, -0.3	<0.001	-0.5	-0.6, -0.3	<0.001	-0.4	-0.6, -0.2	<0.001	-0.3	-0.5, -0.2	<0.001	0.1	0.0, 0.1	<0.001	0.0	0.0, 0.0	0.002
TRT*Time	0.3	0.1, 0.5	<0.001	0.4	0.2, 0.6	0.001	0.3	0.1, 0.5	0.007	0.3	0.1, 0.5	0.005	-0.1	-0.1, 0.0	<0.06	-0.0	-0.0, -0.0	0.008
TRT at any visit	**Mean***	**CI∞**		**Mean***	**CI∞**		**Mean***	**CI∞**		**Mean***	**CI∞**		**Mean***	**CI∞**		**Mean***	**CI∞**	
Yes	32.8	31.3, 34.4		9.7	9.2, 10.3		8.3	7.8, 8.9		13.5	12.9, 14.3		18.9	17.3, 20.4		6.8	6.5, 7.1	
No	36.6	34.8, 38.5		11.5	10.9, 12.2		8.9	8.3, 9.5		14.9	14.1, 15.7		17.0	15.4, 18.6		6.0	5.7, 6.4	

¥ The value presented represents the percent change for a one-unit increase in the effect. This calculated by: [exp(beta) – 1]*100
∞ 95% confidence interval
* Geometric

Significant Covariates by Model:

Total AMS: visit: p<0.0001, treatment*visit: p=0.17, BMI: p<0.0001, age: p=0.03, country: p<0.001, HG type(1º/2º): p=0.03, daily hard physical work: p=0.10, smoking history: p=0.03, self-reported health: p<0.001, previous urologic disorder: p=0.04, current psychiatric disorder: p<0.001, psychiatric disorder meds: p<0.001.

AMS Sexual Symptoms: treatment status: p=0.14, visit: p<0.001, treatment*visit: p=0.004, age: p<0.001, BMI: p=0.02, country: p=0.001, months from HG diagnosis: p=0.11, daily hard physical work: p=0.04, smoking history: p=0.01, self-reported health: p<0.001, previous urologic disorder: p<0.001, psychiatric disorder meds: p<0.001.

AMS Psychological Symptoms: treatment status: p=0.02, visit: p=0.0002, age: p=0.01, BMI: p<0.001, HG type (1º/2º): p=0.01.

AMS Somatic Symptoms: visit: p<0.001, age: p=0.18, BMI: p<0.001, country: p<0.001, months from HG diagnosis: p=0.18, daily hard physical work: p=0.17, HG type (1º/2º): p=0.04, self-reported health: p<0.001, current psychiatric disorder: p<0.001, psychiatric disorder meds: p=0.006.

IIEF Erectile Function: treatment status: p=0.004, visit: p<0.001, treatment*visit: p=0.07, age: p<0.001, modified Charlson Index: p=0.001, country: p<0.001, site specialty: p<0.001, daily hard physical work: p=0.08, self-reported health: p<0.001, family history of prostate cancer: p=0.18, previous urologic disease: p=0.005, current psychiatric disorder: p=0.10, ED meds: p=0.02, psychiatric disorder meds: p=0.006, lipid lower meds: p=0.02.

IIEF Sexual Desire Function: treatment status: p=0.03, visit: p<0.001, age: p=0.04, BMI: p=0.05, country p=0.01, daily hard physical work: p=0.004, self-reported health: p<0.001, family history of prostate cancer: p=0.005, psychiatric disorder meds: p=0.02.

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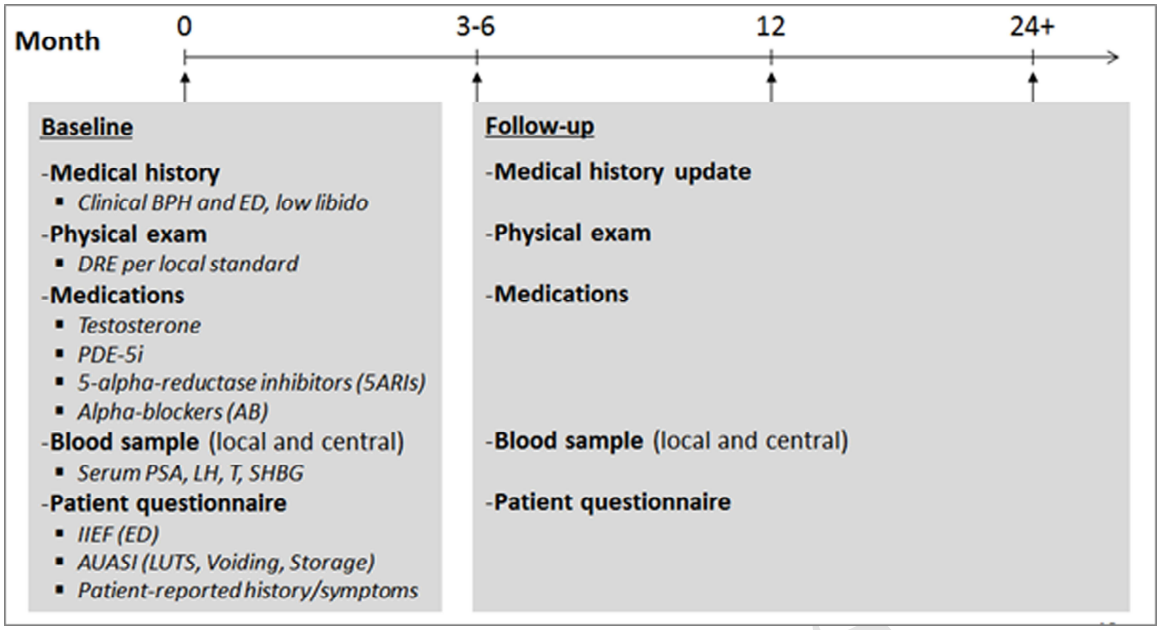

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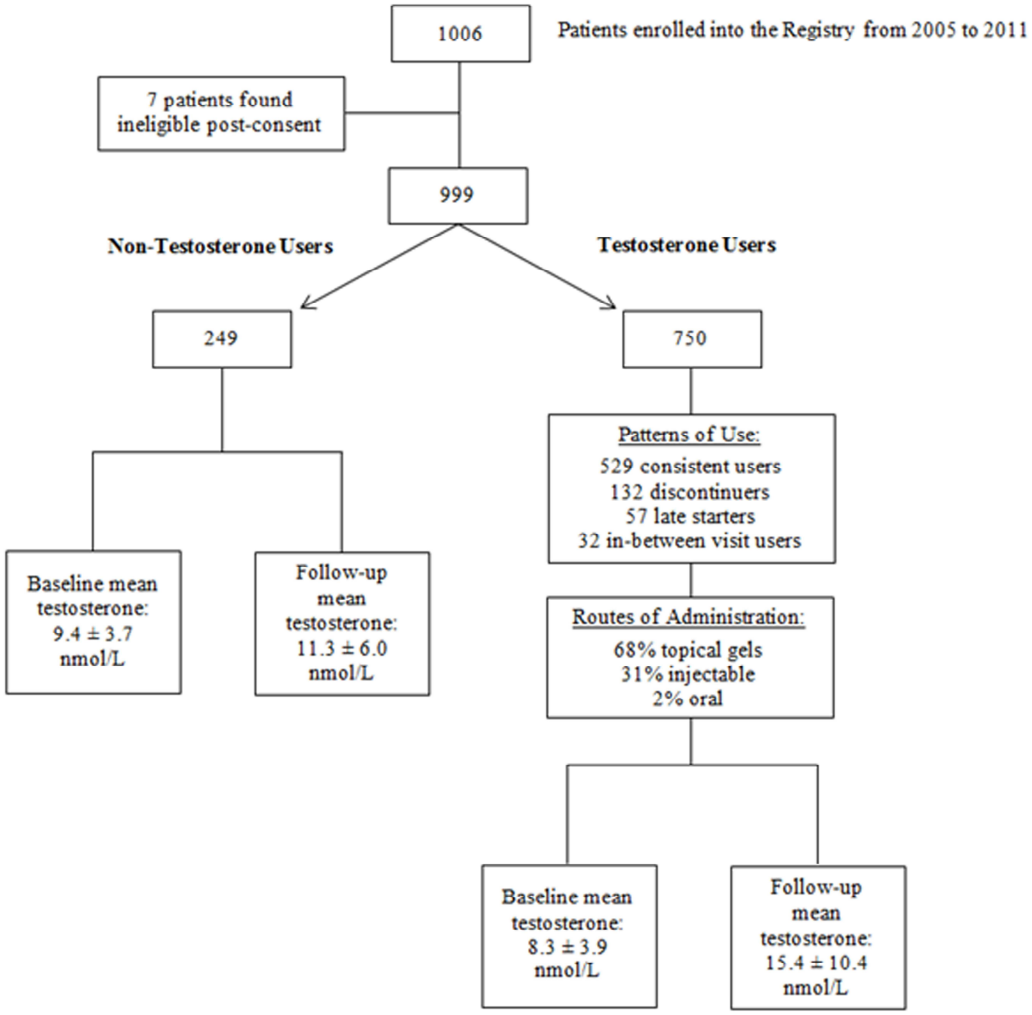
1006
Patients enrolled into the Registry from 2005 to 2011
7 patients found ineligible post-consent
999
Non-Testosterone Users
Testosterone Users
249
750
Baseline mean testosterone: 9.4 ± 3.7 nmol/L
Follow-up mean testosterone: 11.3 ± 6.0 nmol/L
Patterns of Use:
529 consistent users
132 discontinuers
57 late starters
32 in-between visit users
Routes of Administration:
68% topical gels
31% injectable
2% oral
Baseline mean testosterone: 8.3 ± 3.9 nmol/L
Follow-up mean testosterone: 15.4 ± 10.4 nmol/L

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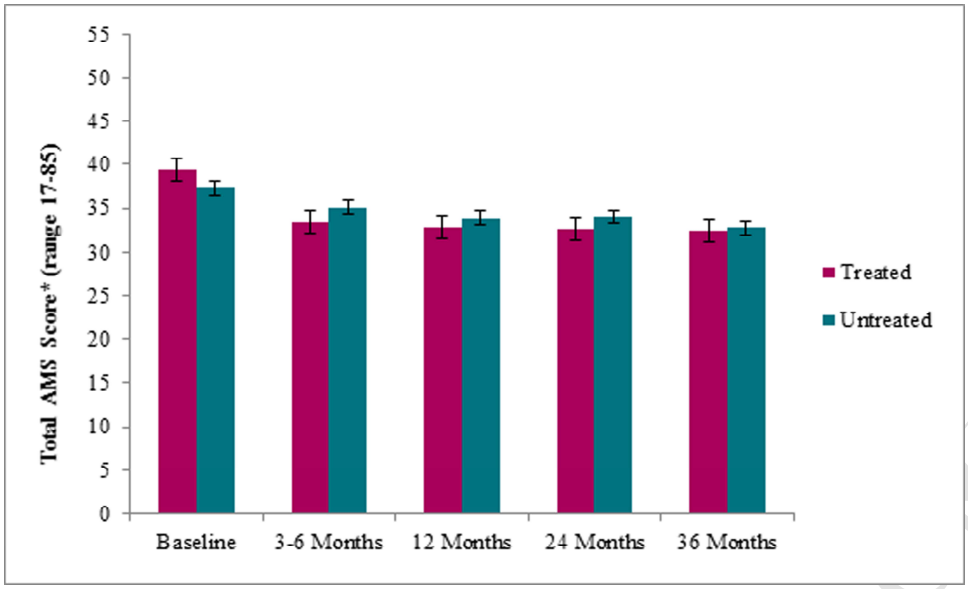

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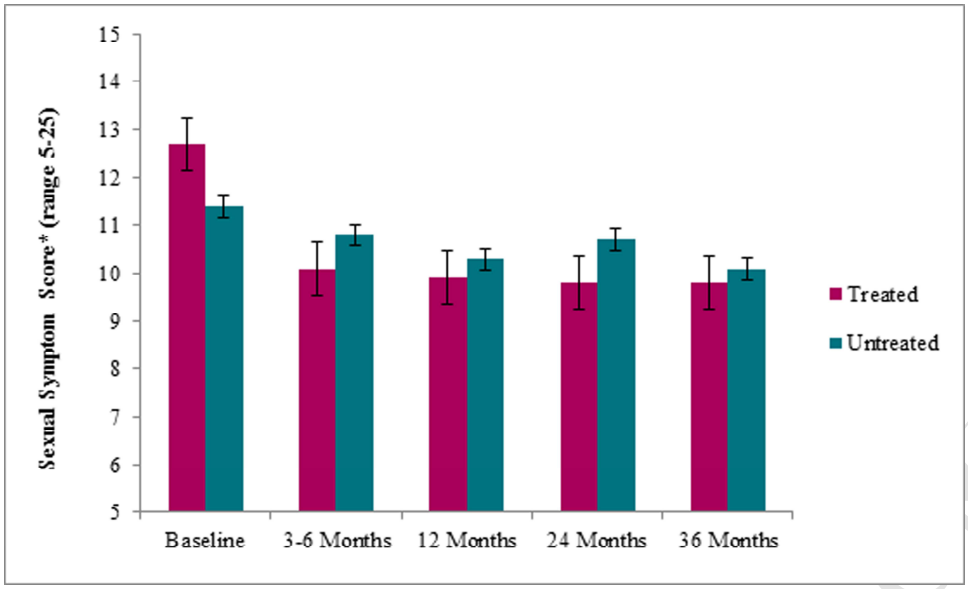

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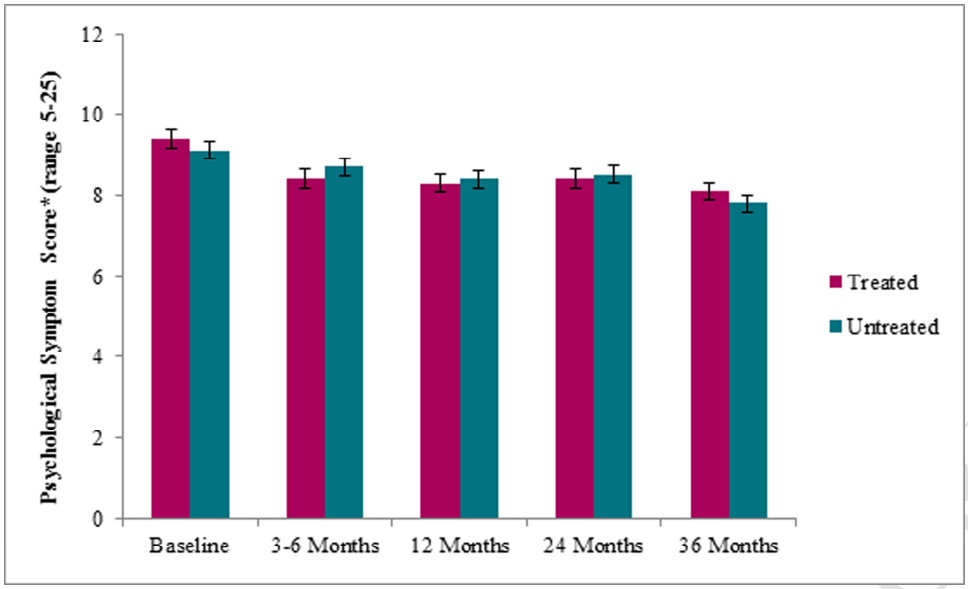

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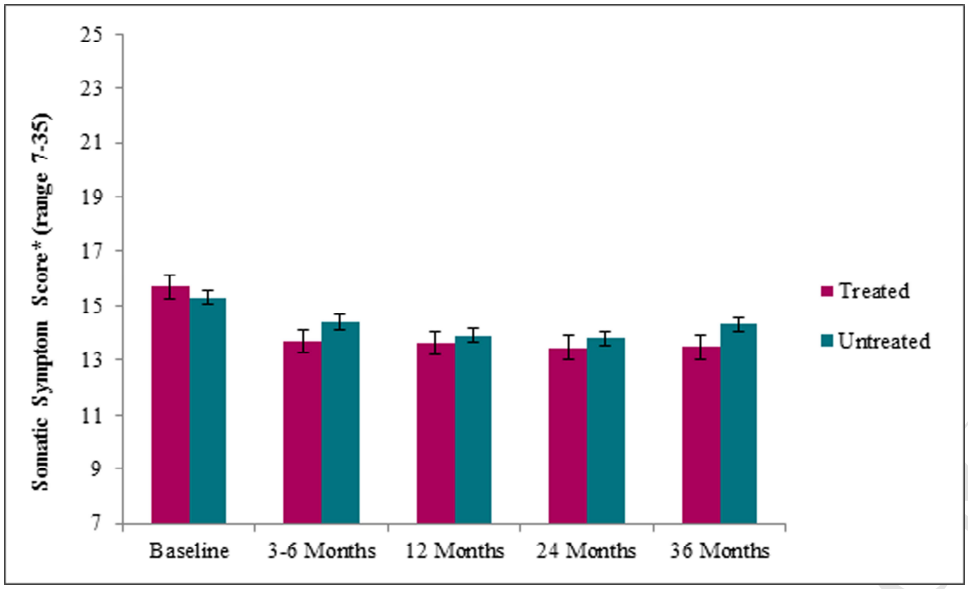

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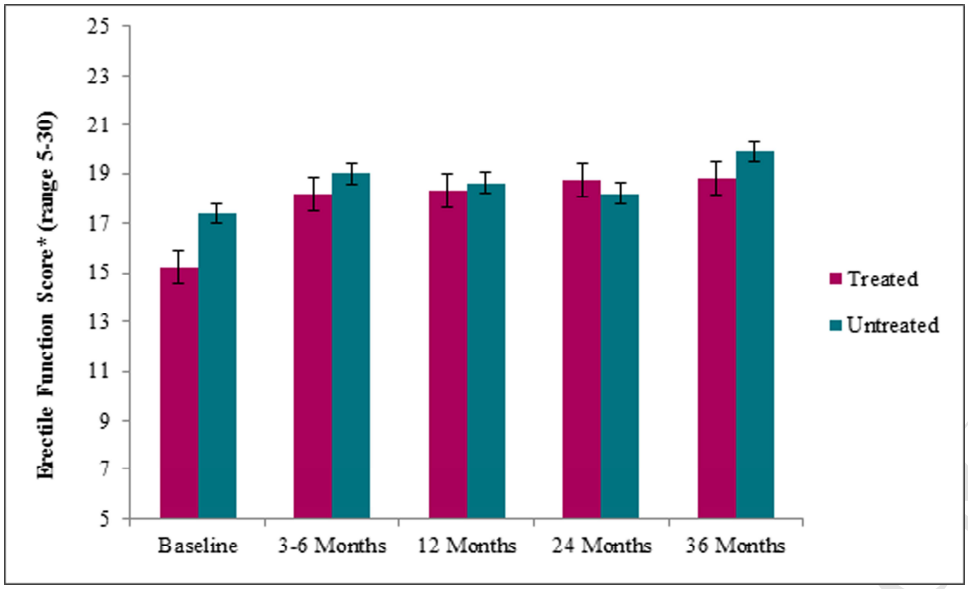

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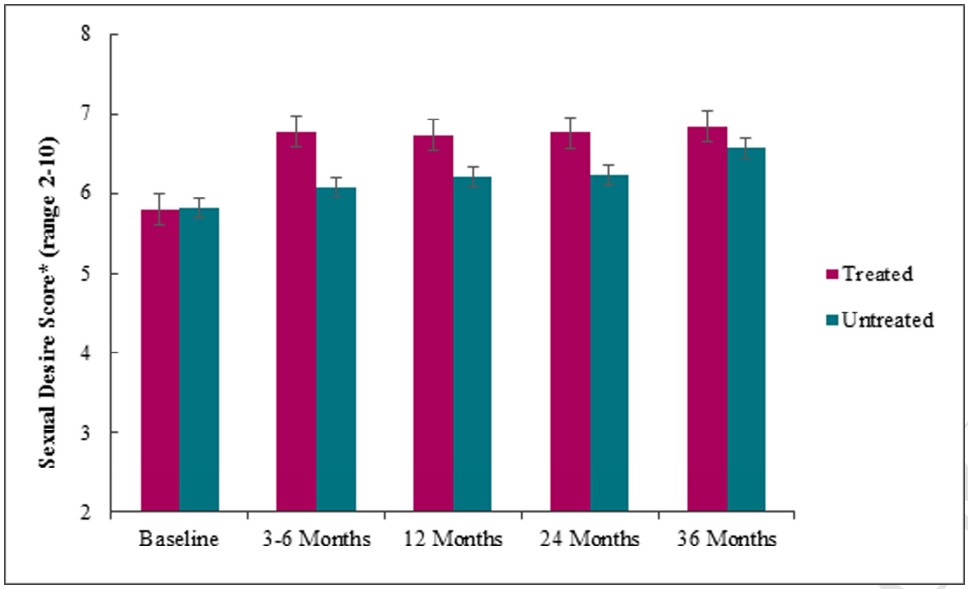

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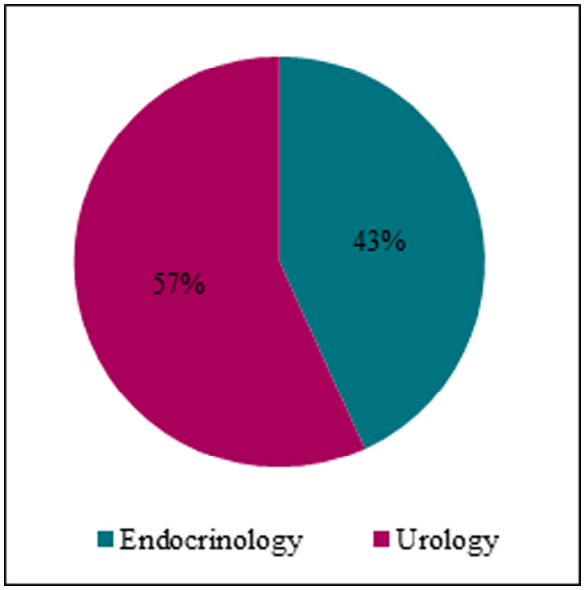

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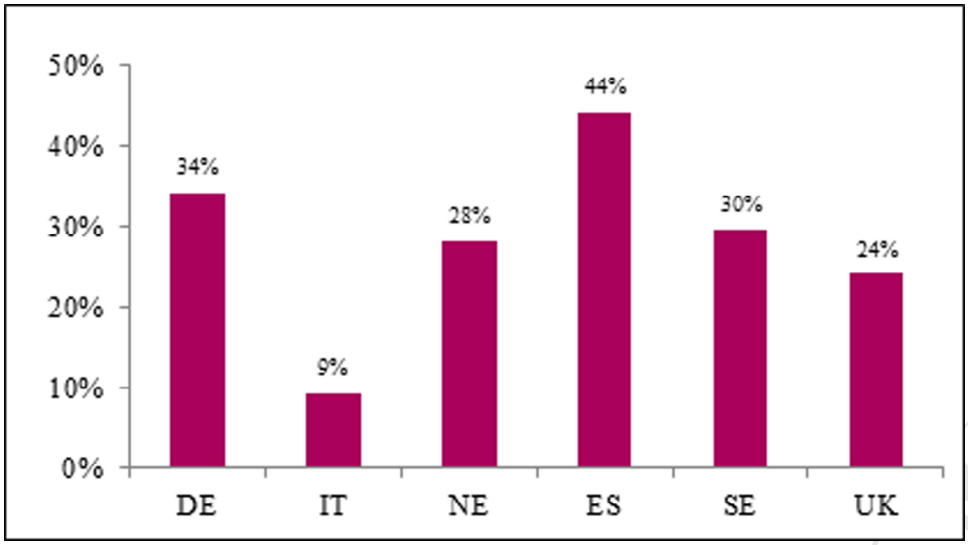

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