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Patient satisfaction with testosterone replacement therapies: the reasons behind the choices

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Abstract

Introduction: Testosterone replacement therapy (TRT) for male hypogonadism is rapidly gaining popularity and acceptance. Options include gels, injections, and implantable subcutaneous pellets.

Aims: To determine rates of patientsatisfaction and reasons forpatient preferences in hypogonadal men on TRT.

Main Outcome Measures: Patient satisfaction responses obtained via anonymous survey.

Methods: An anonymous, prospectivesurvey was distributed to men presenting for TRT at an academic urology clinic. The survey was organized into multiple domains including patient satisfaction and treatment motivation.

Results: Average patient age was 49 ± 0.7 years ($n=382$). Injectable testosterone was chosen by 53%, gel-based regimens by 31%, and pellets by 17%. Overall, 70% of patients were satisfied with their TRT and 14% reported dis-satisfaction. Satisfaction rates were similar between gels (68%), injections (73%), and implantable pellets (70%). Doctor recommendation was the sole significant reason forpatients preferring gel-based TRT (66% vs. 37% injection users vs. 31% pellet users). Injectable TRT was favored due to lower cost (35% vs. 21% gel users vs. 19% pellet users). Pellets were favored forease of use (64% vs. 44% injection users vs. 43% gel users) and convenience (58% vs. 26% injection users vs. 19% gel users).Pellets had increased rates of satisfaction within the first 12 months. Improvements in concentration and moodoccurred at higher percentagesin satisfied patients.

Conclusions: Patients are satisfied with TRT.Lower costs are important to patients on injections. Convenience and ease of use are central in choosing pellet therapy. Men on TRT should be questioned about mood and concentrationsince these factors exhibited the greatest improvements in satisfied patients.

Keywords

Testosterone replacement therapy; patient satisfaction; patient preferences; male hypogonadism

INTRODUCTION

Typified by low serum testosterone levels and pervasive, non-specific symptoms of diminished libido, fatigue, poor concentration, erectile dysfunction, lack of concentration,

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and depressed mood, male hypogonadism is currently characterized as a male health epidemic¹⁻⁵. Indeed, idiopathic age-related declines in testosterone affects a range between 5% and nearly 40% of men^{2, 6} with recognized associations between low levels of testosterone and obesity, diabetes, metabolic syndrome, dyslipidemia, osteoporosis, cardiovascular disease as well as all-cause mortality⁷⁻¹⁷.

Testosterone replacement therapy (TRT) unequivocally increases levels of serum testosterone¹⁸⁻²⁶. In males, prepubertal-onset hypogonadotropic hypogonadism, can also gradually lead to the development of secondary sexual characteristics²⁷. Additionally, clinicians note improvements in quality of life²⁸⁻³² as well as body weight and waist circumference occur^{33, 34}. In recent years, increased awareness of male hypogonadism and the benefits of TRT, partially driven by the media and pharmaceutical marketing strategies, have led more men to seek diagnosis and treatment. In a recent study examining prescribing patterns in the United States, 2.91% of men aged greater than 40 years, and 3.75% of men greater than 60 years of age, were prescribed some form of TRT³⁵. Indeed, the current popularity of TRT is evidenced by the fact that testosterone prescriptions have increased by over 170% since 2007 and 500% since 1993^{6, 36, 37}.

Presently, several American Food and Drug Administration (FDA)-approved methods of TRT exist including transdermal gel formulations, intramuscular injectables, and subcutaneous testosterone pellets. Each modality has its own advantages based upon their method of administration, pharmacokinetic, economic, and safety profiles. For example, while injectable TRT is traditionally cheaper than other methods, it is associated with increased variability in testosterone levels over time²⁴. Specifically, following injection of 200 mg intramuscular testosterone cypionate, a threefold increase in serum testosterone is observed between days 2-5 with basal levels returning by day 13-14²⁴. On the contrary, gel formulations provide more stable testosterone levels³⁸ but tend to be more costly and are possibly transferred to others via skin-to-skin contact³⁹. Implantable subcutaneous pellets (Testopel; Auxilium Pharmaceuticals, Malvern, PA) have the advantage of only requiring treatment every three to four months, but are relatively expensive and negate the ability to control a patient's exogenous testosterone dose within this window of time^{21, 25}. The testosterone formulations discussed within this study are limited to those available only in the United States. Other options for treatment in hypogonadal men include anti-estrogens, selective estrogen receptor modulators as well as human chorionic gonadotropin⁴⁰.

In spite of the rapidly increasing diagnosis of hypogonadism and the acceptance of TRT within the medical community and general population^{21, 24, 25, 41}, the factors contributing to patient preferences and satisfaction with TRT have yet to be described. As such, the current study was devised with the goal of giving physicians a perspective into the reasons why patients in the United States choose specific methods of TRT and how this choice impacts patient satisfaction.

METHODS

Following approval by the Institutional Review Board (IRB), an anonymous, prospective survey was distributed to all patients with a diagnosis of "hypogonadism" listed as the reason for their follow-up clinic appointment. The survey was self-administered in a physician's office waiting room. The physician is a high-volume, academic urologist with a specialization in Andrology located in the United States. As such, all testosterone formulations prescribed, and discussed within the manuscript, are limited to those available in America. Written instructions were provided explaining the purpose of the questionnaire and emphasizing its confidential and anonymous nature. A private and secure drop box was located in the clinic waiting room to assure patients that no physician would have access to

the questionnaire prior to the appointment. The box was locked and emptied daily. The surveys were stored in a secured cabinet with the collected data encrypted on password-protected computers in accordance with IRB policy.

Patients were excluded from analysis if their surveys contained multiple incomplete or conflicting responses and if the respondents indicated that they were not currently using TRT for hypogonadism at the time of survey completion. In some instances, patients documented only certain parameters (i.e. height but not weight). When this occurred, results were compiled using only those patients where complete data were obtained. Within the tables, the number of patients included is listed in parenthesis. For parameters such as for body mass index (BMI) where values were dependent on the patient responding to two questions (i.e. height and weight), the value was not calculated if a patient neglected to answer one of the necessary components.

The survey was designed to assess all patients presenting for TRT and included basic patient demographics such as age, sexual orientation, marital status, level of education, and income. Further questions examined the patient's current modality of TRT and specifically focused on the domains of self-worth, embarrassment, satisfaction and motivation. The majority of the questions produced single-answer responses via multiple choice or yes/no answers. Several questions gave patients the option to provide additional written details. Assessment of energy, libido, mood, muscle mass, and concentration were conducted via self-report. Patients were given a chart and asked to check the most-representative section. The question was phrased as: "Consider the following while on your current testosterone supplement" and the aforementioned aspects were assessed within the context of "No improvement", "Some improvement" and "Lots of improvement". Data were stratified according to patients' self-reports of the modality of TRT currently prescribed.

Data were tabulated and organized using Microsoft Excel (Microsoft, Redmond, WA). Prism 6 and QuickCalcs (GraphPad Software Inc.; La Jolla, CA) were used to perform Chi-square testing, Yates correction, Fisher's exact test and linear regression analysis. A p-value of 0.05 was considered statistically significant and all values were reported as mean \pm SEM unless otherwise noted.

RESULTS

A total of 382 completed surveys were collected and available for analysis. The average patient age was 49.2 ± 0.67 years (**Table 1**). Overall, the patient cohort had an overweight BMI with the majority self-described as college-educated, married, heterosexual and childless with annual income greater than \$75,000 (**Table 1**).

Of the patients who indicated that they were currently on TRT, injectable testosterone formulations were used by 52.5% (n=196), gel-based regimens by 30.6% (n=114), and implantable testosterone pellets by 16.9% (n=63). Overall, 70.4% of patients were satisfied with their current TRT, while 14.0% were dissatisfied (**Figure 1A**). When stratified by the modality of TRT, satisfaction rates were similar between those using gels (68.4%), injections (72.5%) and implantable pellets (69.8%) (**Figure 1B**). The overall number of satisfied patients was significantly greater than those who were in the 'dissatisfied' group (gel: $p < 0.0001$, injection: $p < 0.0001$, pellets: $p = 0.0005$) (**Figure 1B**).

Gel-based regimens were preferred primarily due to 'Doctor Recommendation' (65.7%, **Table 2**). This was significant compared to both injections (37.1%, $p < 0.0001$) and pellet-based TRT (31.3%, $p < 0.0001$) (**Table 2**). Cost was a statistically significant reason for a patient's preference for injectable therapy (34.5%) over gel- (21.3%, $p = 0.023$) and pellet-

(18.8%, $p=0.0264$) based approaches (**Table 2**). Pellet users rated 'ease of use' as the most important reason for their choices (64.1%). This was significantly different from both the injection (43.8%, $p=0.0077$) and gel (42.6%, $p=0.0103$) subgroups (**Table 2**). Similarly, convenience was rated as a reason for preference in 57.8% of pellet-based regimens. This was significantly higher than gel- (19.4%, $p<0.0001$) and injection- (26.3%, $p<0.0001$) based TRT.

Overall patient satisfaction and dissatisfaction did not change with increased duration of TRT (**Table 3**). When the rates within each discrete time-block were compared, patients on pellet-based therapy were significantly less satisfied than those patients on injections ($p=0.02$; **Table 3**) when first beginning therapy (<6 months). Satisfaction rates achieved a plateau between the two modalities after this initial change (**Table 3**). In the 6-12 month time block, patients on pellet-based TRT were significantly more satisfied compared to gel-based TRT ($p=0.03$; **Table 3**). Again, these rates of satisfaction reached a plateau after this point. The rates of patient dissatisfaction were not significantly different at any time point or across any modality of TRT (**Table 3**). When subdivided based upon TRT modality, the most significant change occurred in the group of patients on pellet-based therapy between <6 months and 6-12 months ($p=0.0003$; **Figure 2**). The other modalities of TRT did not exhibit any significant changes over time.

When factors contributing to patient satisfaction with TRT were examined, satisfied patients exhibited higher rates of improvement in all domains assessed (**Figure 3**). Specifically, satisfied patients ($n=266$) reported statistically significant improvements in comparison to dissatisfied patients ($n=53$) in energy (95.5% vs. 79.2%, $p<0.001$), libido (92.9% vs. 77.4%, $p<0.01$), mood (88.7% vs. 67.9%, $p<0.001$), concentration (77.4% vs. 43.4%, $p<0.0001$), and muscle mass (74.1% vs. 56.6%, $p<0.05$). When the net difference was calculated, the percentage of patients reporting improvement in the domains of mood and concentration were the greatest (20.8% and 34% respectively; **Figure 3**).

DISCUSSION

Population-based estimates have identified the prevalence of hypogonadism within the North American population to lie within the 12 to 37% range^{6, 42}. Recent studies have noted that in men 40 years of age or greater, the use of TRT has increased from 0.81% in 2001 to 2.91% in 2011³⁵. Furthermore, the discovery of links between testosterone and numerous disease states such as atherosclerosis and metabolic syndrome^{7, 15-17, 43, 44}, will no doubt contribute to increased TRT prescriptions in the future³⁵.

Numerous methods of TRT are available; however, very few studies²⁵ currently exist to document the reasons why patients choose certain modalities and whether or not they are satisfied with their choices. Very recently, Smith *et al.*²⁵ examined the factors influencing patient decisions to initiate and discontinue subcutaneous testosterone pellets. From that work, it can be inferred that the 28.3% of men who stopped using pellets were dissatisfied²⁵. When this subgroup was looked at in more detail, 50% of the patients cited cost as the primary reason for discontinuation while pain at the time of procedure (18.7%) or persistent pain following implantation (21.8%) were also mentioned. These findings echo those in the current study where cost was a significant reason for a patient's preference for injectable therapy over gel- and pellet-based approaches. Similarly, pellet users in this cohort rated 'ease of use' as the most important reason for their choices. Of the 382 men surveyed in this study, 70.4% reported good overall rates of satisfaction. Similar satisfaction rates were found between the different formulations (i.e. gels, injectables and pellets) suggesting that the vast majority of hypogonadal patients on TRT are happy and experience symptomatic improvements while on TRT.

A recent study noted that 18.63% of first incident users in the United States filled only one prescription; suggesting that this portion of men failed to see any significant improvements³⁵. It is thus tempting to speculate that the patients we found to be ‘very dissatisfied’ (5.3%) and ‘dissatisfied’ (8.7%) were actually captured at the time of their early follow-up appointments. Physicians should thus question patients during their early follow-up visits to ascertain levels of satisfaction. If ‘dissatisfied’, the physician should direct the patient to a more appropriate method of TRT based on individual patient goals; leading to improved symptom control and better rates of satisfaction with fewer dropouts. Other reasons for patient dissatisfaction may lie within the realms of patient physiology and expectations. Previous work has shown that while total serum and free testosterone was highly reproducible within individuals, the differences varied markedly between men⁴⁵. Accordingly, not all individuals perceive symptoms at the same levels of serum testosterone. Furthermore, differently hypogonadal symptoms may improve with varying degrees of rapidity following TRT⁴⁶. As such, the rates of patient dissatisfaction observed in the current study may be affected by an individual patient's desire for symptom improvement in a particular symptom domain. For example, since the effects on sexual interest appear 3 weeks after TRT but the changes in erections/ejaculation may require up to 6 months⁴⁶, patients who desire improvement in the latter may be dissatisfied if it does not occur as promptly as improvements in other symptoms.

Testosterone has been used to treat hypogonadism since the 1930s with a multitude of safe and effective TRT options available⁴⁷. While direct absorptive transdermal skin patch products exist (i.e. Androderm, Watson Pharmaceuticals Inc.), local irritation has proven to be a detriment⁴⁸. Since no oral modalities are currently approved for use in the United States⁴⁹, gels, injectables and implantable pellets represent the currently available forms of TRT. At present, testosterone gels have the highest rate of overall prescription³⁵ but are also known to have high rates of patient drop-out⁵⁰. Gel-based TRT have been specifically shown to improve sexual dysfunction⁵¹ and sub-threshold depression in men with hypogonadism⁵². In the current study, gels were used by 30.6% of patients. Work by Schoenfeld *et al.*⁵⁰ has found that adherence to topical TRT is traditionally low and that by six months post prescription, only 37.4% of men continue on the medication. This number dropped further to 15.4% after 12 months⁵⁰. The reasons for the high discontinuation rates with gels are unknown; however, in our experience, the rates of satisfaction did not vary significantly according to the modality of TRT employed (Figure 1B).

This is less than the 52.5% of patients using injections but greater than the 16.9% using subcutaneous pellets. This is in contrast to the prescribing trends observed using data from the nation's largest commercial American health insurance populations³⁵. It does correspond, however, to the numbers observed in other studies evaluating TRT¹⁸. Indeed, prescribing patterns from American employment-based commercial insurance plans³⁵, cannot be directly extrapolated to general population cohorts, such as the ones seen in the current study, especially in light of our findings that cost plays a significant factor in patients' usage of injectable-based TRT. Furthermore, the findings discussed within this study are limited to those available in the United States. Other types of TRT not available in America, such as long acting testosterone undecanoate, have also shown excellent rates of compliance and improvements in the intercourse and overall satisfaction domains of the International Index of Erectile Function⁵³ as well as consistent losses in body weight, waist circumference and body mass index^{54, 55}.

The current study also found that, in our population cohort, patient preference for gels was largely driven by physician recommendation (Table 2). This was significantly different when compared to injections and pellets. Potential explanations for this may include factors such as ease of use (42.6%) and effectiveness (26.9%). Traditionally, in our practice, we

offer gel-based therapies to older; hypogonadal men who have no young children at home, thus decreasing the risk of transference. Since the average age of our cohort was younger (49.2 years) and a large proportion (35.9%) had young children at home, this may have also influenced our findings in that gel-based TRT may not have been the recommended option.

One limitation that deserves consideration is that this study did not discriminate between the different types of gels currently available. This is important in that previous studies have shown that different gels can have different efficacies²³. Indeed, Grober *et al.*²³ found that 20% of men had a suboptimal clinical or biochemical responses to their initial alcohol-based gel selection²³. The authors attributed this to the pentadecalactone emollient that is specific to Testim^{22, 23} and noted that total and free serum testosterone levels increased after switching from AndroGel to Testim but not from Testim to AndroGel²³. Unfortunately, our study did not capture those men who were testosterone gel non-responders. Given the anonymous nature of the survey, testosterone levels could not be compared. It is therefore possible that unsatisfied patients might have been part of the testosterone 'non-responder' sub-group. A further limitation includes the patient population surveyed. They are highly educated with high incomes (Table 1) and as such, those patient preferences tend to predominate in our patient cohort.

Subcutaneous implantable pellets were used by 16.9% of our patient population. The majority of these patients cited ease of use (64.1%) and convenience (57.8%) as the major reasons for their satisfaction with the product (Table 2). Previous work showed that the majority of patients on pellet-based therapy are typically switched from either gel-, or injectable-based therapies²⁵ but no studies exist documenting satisfaction. The majority of the research on pellet-based TRT has focused on detailing the pharmacokinetics of the delivery system. In one such study, Pastuszak *et al.*²¹ found that men with a body mass index (BMI) >25 kg/m² attained lower testosterone peaks with slower decay pharmacokinetics than men with BMI <25 kg/m² and those with 10-12 pellets implanted exhibited higher levels of estradiol²¹. Another study by McCullough *et al.*²⁰ identified that implantation of greater than six pellets resulted in therapeutic testosterone levels (said to be >300 mg) at 1 month. Patients were then able to maintain this acceptable range for approximately 4-6 months²⁰. Higher pellet levels achieved higher and more consistent levels of testosterone²⁰. Since our study did not stratify patients based on the number of implanted pellets or BMI, it is possible that these factors may have also affected our findings. Furthermore, a previous study by Moisey *et al.*⁵⁶ investigated the kinetics of testosterone following intramuscular injection of testosterone undecanoate. The authors found that body size (i.e. body weight, BMI and body surface area) negatively correlated with total serum testosterone levels; suggesting that men of increased body weight required more testosterone to achieve similar levels⁵⁶. While BMI was recorded in our study population, we did not stratify patient satisfaction results on this basis but future work could easily be conducted to address this issue.

The majority of the patients in the current study were treated with injection-based TRT (52.5%). Interestingly, the main reasons for patient satisfaction on injectable-based TRT were not as clearly defined as those patients on either gel- or pellet-based TRT (Table 2). One factor that was identified as a significant advantage compared to the other modalities of TRT was the cheaper cost of injectable-based TRT (Table 2). Other factors that may contribute include the variability of dosages. For example, one study detailed the use of 100 mg per week at intervals of 1-3 weeks based on patient preference or response¹⁸. In the current study, doses of 200 mg per week were routinely used in the majority of patients. Another aspect to consider is the wide variation of circulating androgen levels resulting from injectable-based TRT. Indeed, as documented by Nankin²⁴, bi-weekly injections of 200 mg testosterone cypionate resulted in rapid highs on days two to five post-injection followed by

a prompt return to baseline by day 13-14. As such, this peak and valley cycling of serum testosterone levels may contribute to a patient's sense of well-being and satisfaction; a factor that should be addressed in future studies.

The current study also revealed that satisfied patients report improvements in the domains of energy, libido, concentration, mood, and muscle mass at a significantly higher rate than patients who are dissatisfied. Concentration and mood appear to be the biggest determinants of patient satisfaction, as these two parameters exhibited the largest percentage of improvement among satisfied patients in comparison to dissatisfied patients. Therefore, it is highly relevant to assess improvement in these two domains during follow-up visits of patients on TRT, especially in dissatisfied patients.

CONCLUSIONS

Hypogonadal patients on TRT have high rates of satisfaction (~70%) that is independent of the modality employed. Gel and pellet-based TRT may be favorable for long-term therapy given the correlation between patient satisfaction and increased duration of treatment. Improvements in mood and concentration are highly important factors in satisfied patients and clinical follow-up should specifically inquire about these symptomatic improvements.

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Abbreviations

BMI	Body mass index
ED	erectile dysfunction
TRT	testosterone replacement therapy

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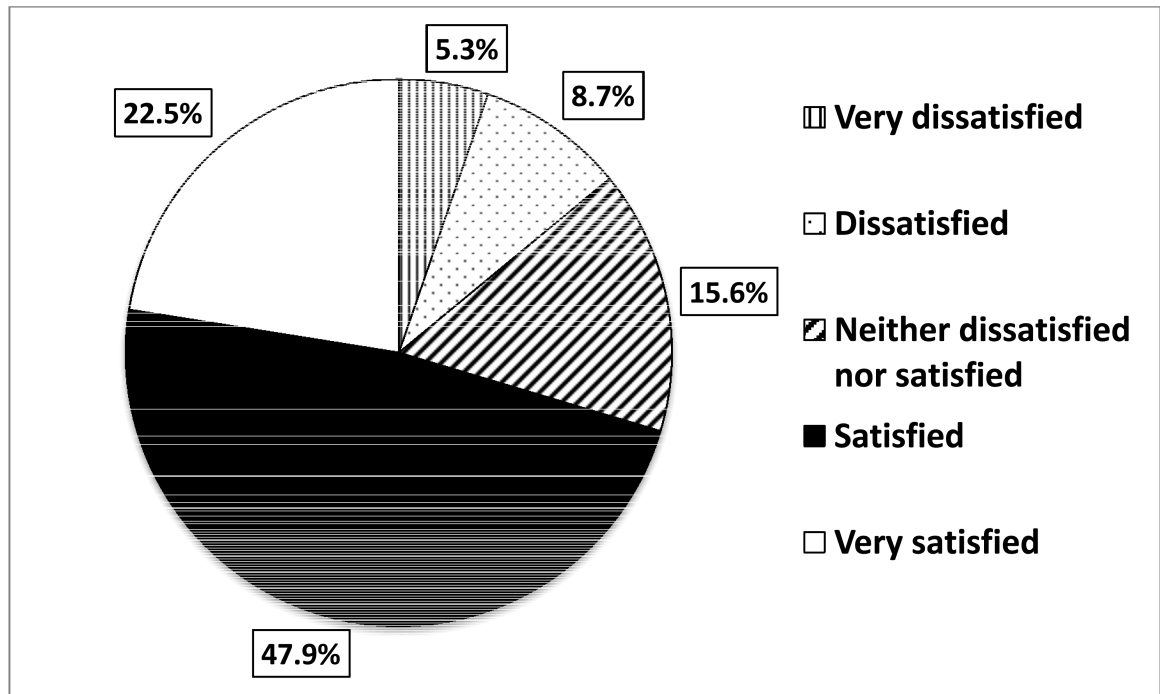


Figure 1A.
Patients on TRT for hypogonadism are highly satisfied overall.

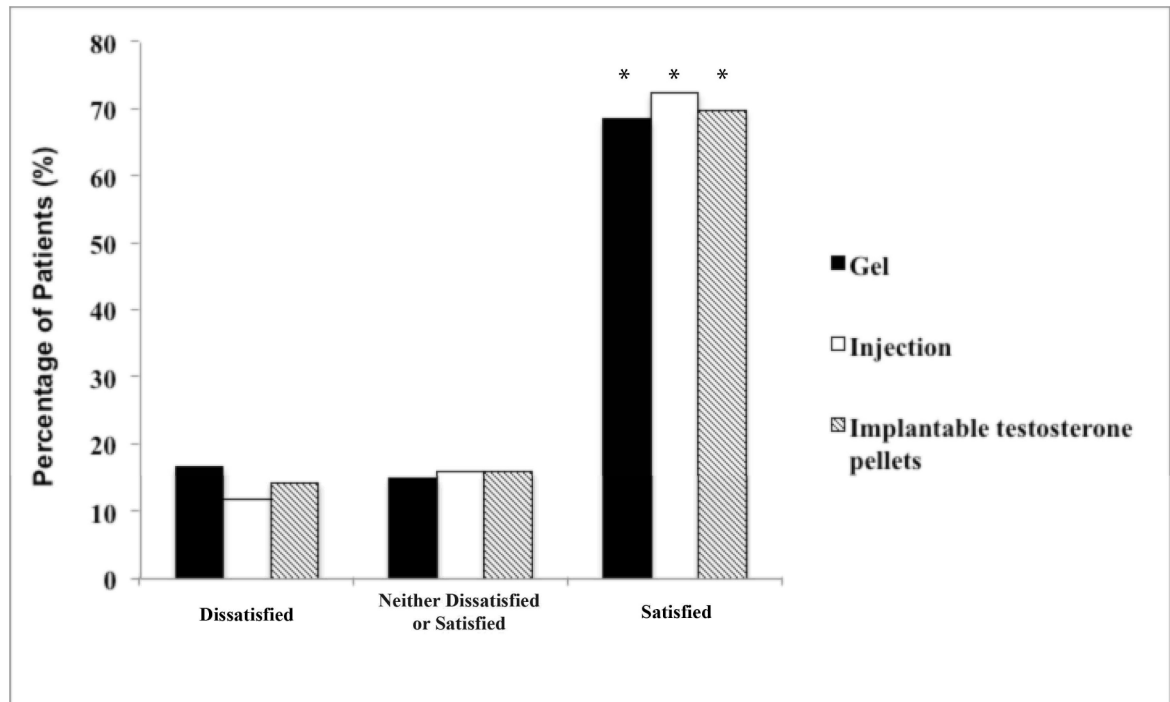
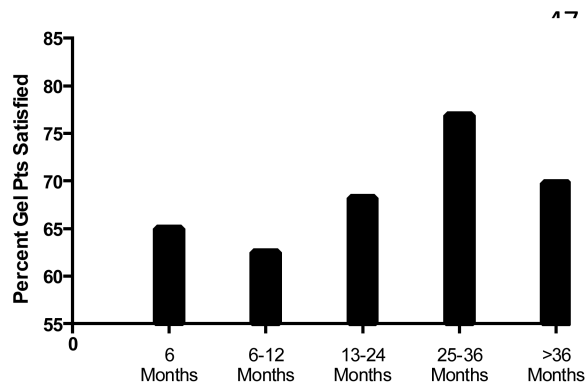
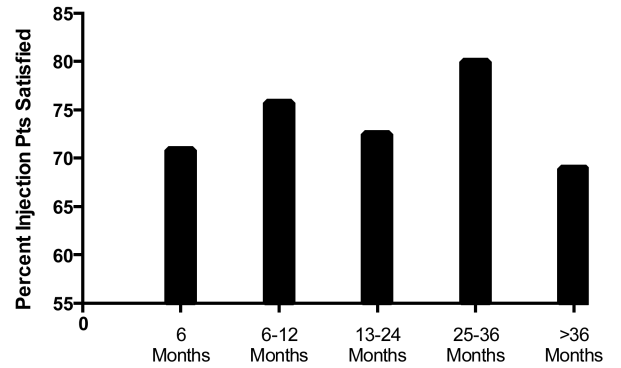
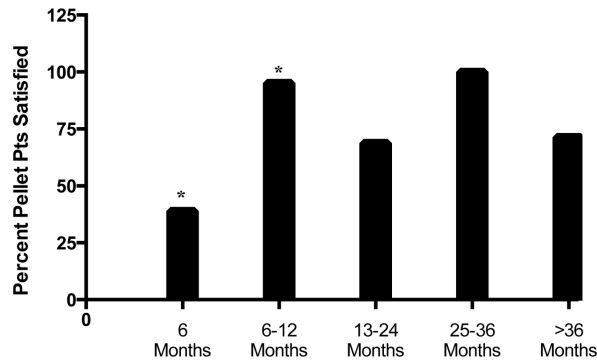


Figure 1B.

Patients are satisfied regardless of the modality of TRT employed (*, $p < 0.05$ for all modalities of TRT when compared to patients who were 'Dissatisfied' and 'Neither Dissatisfied or Satisfied')

A:**B:****C:****Figure 2. Changes in patient satisfaction over time**

Patients on gel- (**Panel A**) and injection (**Panel B**)-based TRT regimens exhibited consistent trends of patient satisfaction over time. Patients on pellet (**Panel C**)-based TRT exhibited a significant (*, $p=0.0003$) improvement from 6 to 6-12 months followed by a plateau in their rates of satisfaction over a 36-month period.

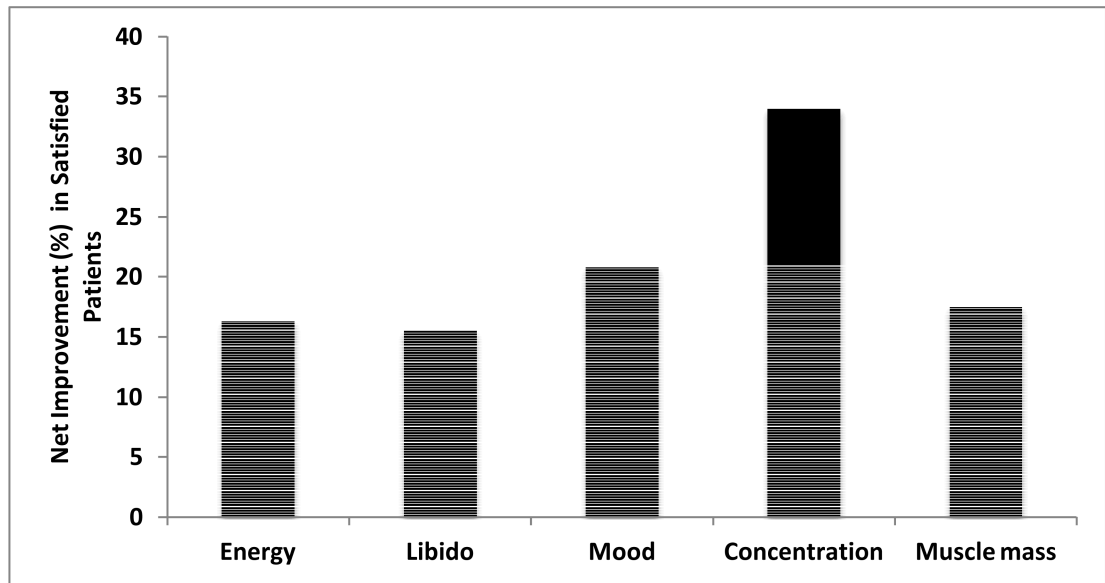


Figure 3.
61 Satisfied patients exhibited the greatest improvements in mood and concentration 62 compared to dissatisfied patients

Table 1

Patient Demographics.

	Patient Cohort
Total number (n)	382
Age at time of evaluation (years±SEM)	49.2±0.67 (n=382)
Weight (kg±SEM)	95.9±0.82 (n=373)
Height (cm±SEM)	180.5±0.37 (n=377)
BMI (kg/m²)	29.4±0.22 (n=373)
Sexual Orientation (n=382): Heterosexual Homosexual Bisexual	96.3% (n=368) 3.4% (n=13) 0.3% (n=1)
Marital Status (n=381): Single Married Divorced Living with partner	15.5% (n=58) 70.8% (n=270) 8.7% (n=33) 5% (n=19)
Number of children at home (n=382): 0 1-2 3-5 >6	57.9% (n=221) 35.9% (n=137) 5.7% (n=22) 0.5% (n=2)
Current Annual Income (n=364): <\$25,000 \$25,000-\$50,000 \$50,001-\$75,000 \$75,001-\$100,000 \$100,001-\$150,000 \$150,000-\$200,000 >\$200,001	3.3% (n=12) 4.1% (n=15) 15.9% (n=58) 21.4% (n=78) 20.1% (n=73) 15.7% (n=57) 19.5% (n=71)
Highest level of education (n=380): Grade School High School Some College/University College/University Graduate Level	0.8% (n=3) 7.9% (n=30) 23.7% (n=90) 41.8% (n=159) 25.8% (n=98)

Table 2

Patient satisfaction 17 with TRT is partially due to factors that are unique to the chosen 18 modality.

Reasons for Preference	Gel (n=108)	Injection (n=194)	Pellet (n=64)
Cost	21.3% (n=23) *	34.5% (n=67) \$,#	18.8% (n=12) *
Ease of use	42.6% (n=46) #	43.8% (n=85) #	64.1% (n=41) *,\$
Ability to raise testosterone levels	26.9% (n=29) *	42.8% (n=83) \$	34.4% (n=22)
Improvement in symptoms	21.3% (n=23) *	41.2% (n=80) \$	32.8% (n=21)
Doctor recommendation	65.7% (n=71) #,*	37.1% (n=72) \$	31.3% (n=20) \$
Concern for transference	0.1% (n=1) *,#	28.4% (n=55) \$	37.5% (n=24) \$
Convenience	19.4% (n=21) #	26.3% (n=51) #	57.8% (n=37) *,\$

A significance of $p < 0.05$ is shown between groups and are depicted as:

* vs. injection,

\$ vs. Gel,

vs. Pellets.

Table 3

Patient satisfaction and dissatisfaction with various modalities of TRT. When each distinct time-point was considered, significance was noted in the rates of satisfaction in patients on Pellets compared to Injections at <6 months as well as between the Gel and Pellet patients at the 6-12 months time point. Rates of dissatisfaction were similar between all modalities.

	<6 months	6-12 months	13-24 months	25-36 months	>36 months
Overall Satisfied Patients (n=264)	62.8% (n=54/86)	78.4% (n=58/74)	70.8% (n=63/89)	79.3% (n=23/29)	69.5% (n=66/95)
Satisfaction based on TRT:					
Gel Satisfied	65.0% (n=13/20)	62.5% (n=10/16) [#]	68.2% (n=15/22)	76.9% (n=10/13)	69.8% (n=30/43)
Gel Dissatisfied	5% (n=1/20)	18.8% (n=3/16)	22.7% (n=5/22)	15.4% (n=2/13)	18.6% (n=8/43)
Pellet Satisfied	38.9% (n=7/18) [*]	95.2% (n=20/21) ^{\$}	68.8% (n=11/16)	100% (n=1/1)	71.4% (n=5/7)
Pellet Dissatisfied	16.7% (n=3/18)	4.8% (n=1/21)	25% (n=4/16)	0% (n=0/1)	14.3% (n=1/7)
Injection Satisfied	70.8% (n=34/48) [#]	75.7% (n=28/37)	72.5% (n=37/51)	80.0% (n=12/15)	68.9% (n=31/45)
Injection Dissatisfied	6.3% (n=3/48)	16.2% (n=6/37)	13.7% (n=7/51)	6.7% (n=1/15)	13.3% (n=6/45)

A significance of $p < 0.05$ was depicted as:

* vs. injection,

^{\$} vs. Gel,

[#] vs. Pellets.