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ABSTRACT

Comparison of Testosterone Replacement Therapy Medications for Treatment of Hypogonadism

Testosterone replacement therapy (TRT) is one treatment option for men with hypogonadism. When TRT is prescribed, effectiveness, patient compliance, cost, and potential side effects should be considered and utilized to develop an individualized treatment plan. Depo-testosterone is the most cost-efficient TRT option and is only administered every 2 weeks which may improve patient compliance, although the dose interval can be adjusted to once per week. Androderm is the most efficacious TRT medication, with up to 92% of patients reaching normal testosterone levels. Testim and Vogelxo have the fewest reported side effects. We recommend depo-testosterone as a first line treatment option.

Comparison of Testosterone Replacement Therapy

Medications in the Treatment of Hypogonadism

Testosterone replacement therapy (TRT) is one possible treatment option for men with hypogonadism and may be beneficial for older men in whom testosterone levels are suboptimal.[1] TRT has been shown to produce a significant improvement in quality of life[2] and may help support cardiovascular health.[3] In addition, when hypogonadal men are treated with TRT, obesity, type 2 diabetes mellitus, and exercise capacity may improve.[3]

When TRT is a viable treatment option, routes of administration, effectiveness, cost, and potential side effects should be considered. In US pharmacies, TRT is available via intramuscular, nasal, buccal, and topical routes. The purpose of this article is to review TRT medications the patient can self-administer and then compare their effectiveness, likelihood of promoting patient compliance, monthly cost (before insurance), and potential side effects.

Methods

Six electronic databases were searched to identify studies and literature reviews relating to TRT efficacy, side effects, and cost. Databases included *CINAHL, MEDLINE, Pubmed, Cochrane Library, Health Source: Nursing/Academic Edition,* and *Web of Science*. *UpToDate* and *Epocrates* were also reviewed.

Research published from 2011-2016 in English was included initially, but yielded few published studies. While the majority of data were published from 2000-2011, one sentinel study was published in 1997. Therefore, inclusion criteria were expanded to include published articles from 1997-2016.

Research focused on US TRT prescription medications the patient could self-administer. Efficacy and side effects were unavailable for some medications in the literature, necessitating

inclusion of data from the package inserts as published either on the Food and Drug Administration (FDA) website or the manufacturer website. To differentiate independently funded studies from manufacturer data, the terms "independently evaluate" and "independent" are utilized. Search terms included: hypogonadism, testosterone, testosterone replacement therapy, efficacy, cost, price, and low testosterone.

Results

Ten studies met inclusion criteria: five studies independently evaluated the efficacy and side effects of a single TRT medication[4-8] and five studies compared the efficacy and side effects of two or more TRT medications.[9-13] The product monograph was evaluated for all 13 prescription medications for all delivery routes and strengths.

Testosterone Replacement Therapy Precautions

TRT may not be appropriate for some patients, namely those with breast or prostate cancer, a prostate nodule or induration, or a prostate specific antigen (PSA) above 4 ng/ml or above 3 ng/ml in male patients at high risk for prostate cancer. TRT is contraindicated in men who have a hematocrit higher than 50%, severe obstructive and untreated sleep apnea, severe urinary tract symptoms, or heart failure.[14]

Adverse effects occur with any TRT medication and include: 1) erythrocytosis; 2) urinary retention; 3) acne; 4) reduced sperm production/infertility; and 5) testicular atrophy/failure, although most of these adverse effects are dose dependent.[15-16] Any male patient wanting more children should be carefully informed of the risks with TRT medication and infertility and testicular atrophy/failure. Less common side effects include: 1) gynecomastia; 2) adrenergic alopecia; 3) worsening benign prostatic hyperplasia; 4) obstructive sleep apnea (OSA) or worsening of already existing OSA; 5) fluid retention; 6) growth of an already existing prostate

cancer; and 7) breast cancer.[15-16] Practice guidelines for monitoring patients after initiation of TRT are available through the Endocrine Society at https://www.endocrine.org/education-and-practice-management/clinical-practice-guidelines

Injectable Testosterone

Depo-testosterone (testosterone cypionate). Depo-testosterone is the most popularly prescribed TRT medication in the US[17] and is a long-acting testosterone commonly prescribed once every 2-weeks. The most common dose is 200 milligrams (mg) in 1 milliliter (ml)[18] although it is available in two doses: 100 mg/ml and 200 mg/ml. The 100 mg/ml is available in a 10 ml vial, while the 200 mg/ml is available in 10 ml vial or 1 ml vial. When calculated from the most commonly prescribed dose, the average cost per month is $22.70 for the 100 mg/ml (10 ml vial) and $18.45 for the 200 mg/ml (10 ml vial).[19] The 200 mg/ml in the 1 ml vial is considerably more expensive at $98.07/month (See Table 1).[19]

Depo-testosterone is commonly prescribed in the US and has been used safely since receiving FDA approval in 1979, however the literature is scarce regarding its effectiveness and side effects. The benefit of depo-testosterone is the twice monthly dosing, however, the disadvantage of intramuscular administration may negatively affect patient compliance.[18] When administered, testosterone levels quickly increase and then gradually decrease until the next injection. Thus, there may be fluctuations in testosterone levels. This variability can be minimized by shortening the amount of time between injections (i.e. 100 mg/week rather than 200 mg/every other week).[18]

Delatestryl (testosterone enanthate). Delatestryl is a long-lasting testosterone injection that only needs to be administered approximately every 2-weeks. Delatestryl has been used for TRT for decades and is available at 200 mg/ml in a 5 ml vial. The most commonly prescribed

dose is 1 ml every 2-weeks. Deletestryl is available as a generic and costs, on average, $23.46/month (See Table 1).[19]

Generally, Delatestryl is well tolerated by patients. Adverse reactions are rarely reported but include the potential for anaphylaxis. Thus, patients should be observed immediately following the injection for any signs of anaphylaxis. Benefits of Delatestryl for TRT include twice/month dosing although the need for regular injections may affect patient compliance.[20] Since 2014, Deletestryl has been in short supply and may be difficult to obtain.[21]

Nasal Testosterone

Natesto, a testosterone-based nasal gel, is self-administered three times per day. Approximately 40 minutes after administration, testosterone levels return to normal, although Natesto's half-life is widely variable, between 10 and 100 minutes.[5] Each bottle of Natesto delivers approximately 60 actuations but, when taken as commonly prescribed, 180 actuations constitute a 1-month supply, therefore, three bottles are needed each month. Natesto is not available in generic form and costs $233.07 per bottle or $699.21 per month (See Table 1).[17]

According to a study funded by the manufacturer, side effects occurred in <9% of patients during the 180-day clinical trial and most commonly included nasopharyngitis, rhinorrhea, parosmia, headache and nasal discomfort and scabbing (See Table 2).[20] Benefits of Natesto include a less invasive delivery method and less risk of inadvertently transferring the gel to a partner or child.[18] One notable disadvantage of Natesto is the three times per day dosing, which may be inconvenient for some patients.[18]

Buccal Testosterone

Striant, the only available buccal form of testosterone, is available in a 30 mg tablet and commonly prescribed twice per day.[19] Manufacturer data from one 12-week clinical study

showed Striant provided steady testosterone levels for 86.6% of subjects.[20] The most common side effect in long-term extension trials was gingivitis (32.6%). Other side effects occurred in <10% of subjects but included gum irritation/pain/edema, bitter taste, and headache (See Table 2). [20] With no generic substitute, the average cost for a 1-month supply of Striant is $724.77 (See Table 1).[19] Advantages to buccal testosterone include quick delivery of medication using a less invasive method.

Two head-to-head comparison studies measuring serum total testosterone levels have been published on Striant[9,11] one of which compared Striant to the Androderm patch[11] and the second of which compared Striant to Androgel 1% packets.[9] The mean total testosterone level was similar between Striant and Androgel.[9] However, Korbonits et al.[11] concluded that Striant was superior to the Androderm patch because Striant testosterone levels were always within normal limits whereas Androderm testosterone levels fell below normal within the first 2 hours of placing the patch (See Table 2).

Two additional independent studies have been conducted with Striant.[6,8] In both studies, Striant was found to effectively elevate serum testosterone levels within 24 hours of initiating treatment.[6,8] No side effects were reported in one study;[6] however, 16.3% of subjects in the Wang, Swerdloff, et al. study reported gum-related irritation.[8]

Transdermal Testosterone

Androderm patch. The Androderm patch is available in two different strengths: 2 mg and 4 mg.[22] The patch should be applied to non-scrotal skin and then replaced every 24 hours, rotating sites with each application. The per month cost of Androderm is $195.03 for 30 patches (See Table 1).[19]

Manufacturer data show Androderm produces normal testosterone levels in 92% of patients.[20] When compared to Deletestryl (testosterone enanthate) in a 6-month trial, Androderm normalized testosterone in 82% of subjects while Deletestryl normalized testosterone for 72% of subjects.[20] However, 37% of patients using Androderm had pruritis at the application site and 12% had a burn-like blister that formed under the patch (See Table 2).[20]

One independent study found Androderm to normalize testosterone levels in subjects, as well as mimic the natural circadian pattern of testosterone during a day.[4] However, Androderm also caused skin irritation in 56% of subjects and burn-like blisters at the application site in 18% of subjects.[4]

Korbonits et al.[12] found that although Striant and Androderm both returned testosterone levels to normal; however, over a 24 hour treatment period subjects receiving Striant maintained normal testosterone levels whereas subjects receiving Androderm had lower than normal testosterone levels within the first 2 hours of applying the patch. For this reason, and because there were few side effects in either group, Korbonits et al. concluded that Striant was superior to Androderm (See Table 2).[11]

In two additional independent studies, Androderm was compared to Testim[13] and Androgel.[12] Steidle et al.[13] concluded that treatment with two Testim 1% gel tubes per day (100 mg total) was superior to Androderm in normalizing testosterone levels and had fewer dermal-related side effects, such as erythema, rash, pruritis, and irritation. Mazer et al.[12] reported similar efficacy and localized skin-related side effects between Androderm and Androgel (See Table 2).

Gel pumps/packets/tubes. When transdermal testosterone gel is prescribed as a pump, the most common dosing schedule is 2-4 pumps each day. Packets and tubes are both designed for single use, meaning a 1-month supply would take 30 packets or 30 tubes.

Androgel is available in a pump and packet form at 1% or 1.62% doses. Similarly, Fortesta 2% and Axiron 2% are available as a pump. Vogelxo 1% is available as a pump, a packet, and a tube. Testim 1% is only available in tubes. All transdermal gel formulations carry the risk of unintentionally transferring medication to a partner or children (See Table 2).

Average cost for a 1-month supply of testosterone gel pumps/packets/tubes varies. The most expensive testosterone gel is Axiron 2% pump at $630.78.[19] The next most expensive testosterone gel is Androgel costing $516.41 for the 1.62% packets and $510.77 for the 1.62% pump.[17] All remaining formulas are similar in price for a 1-month supply (See Table 1).[17]

Four independent studies compared the efficacy and side effects of testosterone gel in packets and tubes to other testosterone medications.[9,10,12,13] Androgel was found to have similar efficacy and occurrence of side effects when compared to Striant and Androderm.[9,12] When comparing Testim to Androderm, Testim was superior at achieving normal testosterone levels and had a lower incidence of side effects.[13] In a crossover study comparing Androgel and Testim, researchers concluded that Testim was more efficacious than Androgel although Androgel had fewer side effects (See Table 2).[10]

Wang, Cunningham, et al.[7] compared the efficacy of Androgel 1% packets in varying doses (ie 1 or 2 packets daily) by examining mean serum and free testosterone levels. When titrated, Androgel 1% packets resulted in patient outcomes similar to injectable testosterone or other transdermal formulas.[7] Additionally, Androgel 1% gel packets did not cause skin irritation and were found to be safe and effective, even in long-term treatment.[7]

Manufacturer data regarding efficacy were also reviewed. Axiron was the most effective gel resulting in normal testosterone levels in 89% of subjects. Effectiveness of Androgel 1% and 1.62% was reported as 87% and 81.6% after titration, respectively. Fortesta was efficacious in

77.5% of subjects and Testim and Volgelxo resulted in normal testosterone levels in 74% of subjects after titration.[20]

Package insert information regarding side effects of Testim, Vogelxo, Axiron, Fortesta, and Androgel 1% and 1.62% were reviewed. Testim and Vogelxo had the least occurrence of side effects ($\leq$5%) the most common of which was skin irritation. With Axiron and Androgel 1% and 1.62% side effects were found in less than 10% of subjects. The most common side effect of Axiron was skin irritation while acne was the most common side effect of Androgel 1% and 1.62%. Finally, Fortesta had the highest occurrence of side effects at 17%, the most common of which was skin irritation (See Table 2).[20]

Discussion

TRT medications administered every day most consistently maintain testosterone levels within a normal range. Since all transdermal TRT medications are prescribed on a once per day dosing schedule, it would appear that transdermal TRT preparations, in general, are more efficacious than TRT medications with more frequent or less frequent dosing schedules.

Compliance is another consideration when prescribing TRT for patients since the number of medication doses each day can have a significant effect on patient compliance. Indeed, there is an inverse relationship between the number of medication doses and patient compliance: the higher the number of medication doses in a day, the lower the patient compliance.[23] Some testosterone medications, such as Natesto and Striant, are prescribed three times per day or two times per day, respectively, and may negatively affect patient compliance. Using this same logic, it would seem that depo-testosterone and Delatestryl would be associated with greater patient compliance because these two injected testosterone medications only need to be administered every 2-weeks.

A review of all testosterone medications revealed that the most cost-efficient TRT medications were injectable formulations, namely depo-testosterone and Delatestryl. Depo-testosterone is commonly prescribed at 200mg/ml every 2-weeks and is available for dispense in a 10ml vial for $92.29[19], although there is variation among some prescribers regarding the dose interval. For example, some providers opt to prescribe 100mg every week to avert the medication trough that can occur with every other week dosing. The 10ml vial of depo-testosterone, however, would have enough medication for 5-months, for an average monthly cost of $18.45. In comparison, Delatestryl is commonly prescribed at 200mg/ml every 2-weeks and can be dispensed in a 5ml vial for $23.46.[17] The 5ml vial of Delatestryl would contain enough doses for 2.5-months for an average monthly cost of $23.46. When compared to the cost of transdermal patches at $195.03 per month or the cost of nasal gel at $699.21 per month, the cost difference is notable (See Table 1).

Finally, side effects of each TRT medication should be carefully evaluated. The injectable testosterone depo-testosterone is not well studied, even though it has been available the longest and is the most frequently prescribed of all types of TRT medications with seemingly few side effects. Less than 9% of Natesto users experience side effects which are usually associated with the nasopharynx, such as nasopharyngitis. Over 32% of patients taking Striant report gingivitis as a side effect (See Table 2).[20]

There are also side effects with transdermal testosterone medications. Androderm has the highest occurrence of side effects with up to 56% of patients reporting skin irritation[4] (See Table 2), and 12-18% reporting a burn-like blister at the application site.[20] The greatest concern regarding the testosterone transdermal gel is unintentional transdermal transfer to children or women.[20] Androgel 1.62% manufacturer data show that average testosterone levels in female

partners increased by 280% after contact with the application site. However, when the application site was covered by a shirt, average testosterone levels in female partners increased by only 6-13%. Testim is the only transdermal testosterone that showed no change in female partner testosterone levels after covering the application site with a shirt.[20]

Implications for Nurse Practitioners

The Endocrine Society[4] recommends healthcare providers select a TRT with consideration of which medication effectively stabilizes testosterone levels, aligns with patient preference (increasing compliance), is affordable, and causes the fewest side effects. Depo-testosterone is the most affordable TRT medication and has the highest compliance, assuming the patient can tolerate injections. Therefore, depo-testosterone may be a good first line therapy option. Depo-testosterone may not control testosterone levels as tightly as the transdermal testosterone that is administered every day because it is only injected once every 2-weeks. For patients who are sensitive to the testosterone peaks and troughs of depo-testosterone, we recommend altering the administration schedule to a half dose every week rather than a full dose every 2-weeks.

Androderm patches have the highest efficacy (up to 92%)[20] and are a good second line therapy option for patients who cannot tolerate injections. Androderm patches are the next most affordable TRT option and offer consistent dosing without the peaks and troughs of injected testosterone. However, the patient should be warned about the risk of side effects, namely skin irritation.[4]

For patients who cannot tolerate depo-testosterone injections or the Androderm patch, we recommend Testim gel as a third line option. Testim is the next most affordable TRT option, has an efficacy of 74%[20], and is associated with fewer side effects than Androderm.[4,20] All TRT gel

medications carry the risk for unintentional transfer to a partner or to children, although according to research Testim has the lowest risk of unintentional transfer as long as the application site is covered with a shirt.[20]

Limitations/Further Research

Few independent research studies have been published in the last 5 years. Additionally, medication costs may vary between states and pharmacies and can be affected by insurance coverage. All patients taking TRT medications need labs, which would necessitate further cost. Furthermore, injected TRT medications may warrant a clinic visit to administer the medication, unless the patient and/or family can administer injections. Finally, patients receiving injected TRT may need an altered dosing schedule such as a half dose every week rather than a full dose every other week.

Conclusion

There are different TRT treatment options that should be selected with careful consideration of efficacy, compliance, cost, and side effects. All methods of testosterone delivery improve patient testosterone levels. In consideration of TRT medication efficacy, patient compliance, medication cost, and common medication side effects, we recommend depo-testosterone, Androderm, and Testim as the first, second, and third line treatment option.

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Table 1

Types of Testosterone Medications

Trade Name	Generic	Route	Available Dosing	Common Dose	Common Frequency	Average Cost/Month (calculated from common dose)
			Injectable			
depo-testosterone	testosterone cypionate	IM	100 mg/ml 200 mg/ml	200 mg/ml[19]	Q 2 weeks	100mg/ml (10ml vial) = $22.70[19] 200mg/ml (10ml vial) = $18.45[19] 200mg/ml (1ml vial) = $98.07[19]
Delatestryl	testosterone enanthate	IM	200 mg/ml	200 mg/ml[17]	Q 2 weeks	200mg/ml (5ml vial) = $23.46[17]
			Nasal			
Natesto	N/A	Nasal gel	5.5 mg each actuation	11 mg (1 actuation per nostril) [17]	TID	3 bottles (30 days) = $699.21[17]
			Buccal			
Striant	N/A	Buccal	30 mg	30 mg[19]	BID	60 tablets = $724.77[19]
			Transdermal Patch			
Androderm	N/A	Patch	2 mg 4 mg	4 mg[22]	QD	30 patches = $195.03[19]
			Transdermal Gel Pump			
AndroGel 1% or	testosterone 1%	Gel pump	1%-12.5mg/1.25g	50mg (4 pumps)[19]	QD	2 bottles 1% (30 days) $309.24[17]
1.62%	testosterone 1.62%		1.62%-20.25mg/1.25g	40.5mg (2 pumps)[19]		1 bottle 1.62% (30 days) $510.77[17]
Axiron 2%	N/A	Gel pump	30mg /1.5ml	60 mg (2 pumps) [19]	QD	1 bottle (30 days) $630.78 [19]
Fortesta 2%	testosterone 2%	Gel pump	10mg/0.5g	40mg (4 pumps) [2]	QD	1 bottle (30 days) = $281.80[17]
Vogelxo 1%	testosterone 1%	Gel pump	12.5 mg/1.25g	50mg (4 pumps)[17]	QD	2 bottles (30 days) = $283.69[17]
			Transdermal Gel Packets			
AndroGel 1% or	testosterone 1%	Gel packet	1%-25mg/2.5g 1%-50mg/5g	50mg (1 packet)[19]	QD	30 packets 1% = $309.25[17]
1.62%	testosterone 1.62%		1.62%-20.25mg/1.25g 1.62%-40.5mg/2.5g	40.5mg (1 packet)[19]		30 packets 1.62% = $516.41[17]
Vogelxo 1%	testosterone 1%	Gel packet	1%-25mg/2.5g 1%-50mg/5g	50mg (1 packet) [19]	QD	30 packets 1% = $270.30[17]

Transdermal Gel Tubes						
Testim 1%	testosterone 1%	Gel tube	50mg/5g	50mg[17]	QD	30 tubes = $268.25[17]
Vogelxo 1%	testosterone 1%	Gel tube	50mg/5g	50mg[19]	QD	30 tubes = $268.25[17]

Table 2

Testosterone Medication Comparison

Trade Name	Advantages	Disadvantages	Efficacy in Comparison Studies	Side Effects in Comparison Studies
		Injectable		
depo-testosterone	Q 2 weeks; three-fold increase in testosterone within 2 days; most affordable[19]	IM[20]; levels gradually decrease until next injection	Equal to AndroGel[7]	
Delatestryl	≥72% effective[20]; affordable[17]	IM[20]; in short supply[21]	Equal to AndroGel[7]	
		Nasal		
Natesto	Levels normalize in 40 minutes[5]; less invasive	Upper respiratory side effects in <9% of patients[20]; TID dosing[18]; cost[17]		
		Buccal		
Striant	≥86.6% effective[20]; levels normalize in 24 hours[6,8]; less invasive	Gingivitis in ≥32.6% of patients[20]; BID dosing[19]; most expensive[19]	Superior to Androderm[11] Equal to AndroGel[9]	Equal to AndroGel[9]
		Transdermal Patch		
Androderm	≥92% effective[20]; two doses for titration[22]; mimics natural circadian pattern of testosterone[4]; more affordable than all medications except IM testosterone[19]	Skin irritation in ≥56% of patients[4]; lower than normal testosterone within first 2 hours of application[11]	Superior to Deletestryl[20] Equal to Androgel[12]	Equal to Androgel[12]
		Transdermal Gel		
AndroGel	≥87% effective; two doses for titration; less skin irritation compared to some IM and transdermal formulas[7]	Risk for unintentional transfer[20]; side effects in <10% of patients (acne most common)[20]; restrictions on bathing/swimming[20]	Equal to Androderm[12] Equal to depo-testosterone[7] Equal to Deletestryl[7] Equal to Striant[9]	Equal to Androderm[12] Equal to Striant[9] Fewer side effects than Testim[10]

Axiron	≥89% effective[20]	Risk for unintentional transfer[20]; most expensive transdermal gel[19]; side effects in <10% of patients[20]; restrictions on bathing/swimming[20]		
Fortesta	≥77.5% effective[20]	Risk for unintentional transfer[20]; side effects in ≥17% of patients[20]; restrictions on bathing/swimming[20]		
Vogelxo	≥74% effective[20]	Risk for unintentional transfer[20]; side effects in <5% of patients[20]; restrictions on bathing/swimming[20]		
Testim	≥74% effective[20]	Risk for unintentional transfer[20]; side effects in <5% of patients[20]; restrictions on bathing/swimming[20]	Superior to Androderm[13] Superior to AndroGel[10]	Fewer side effects than Androderm[13]